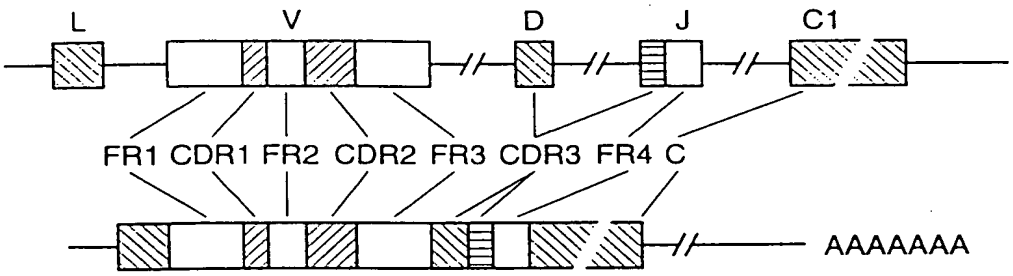


FIG. 1

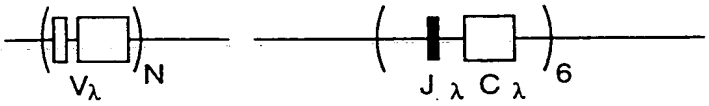


FIG. 2

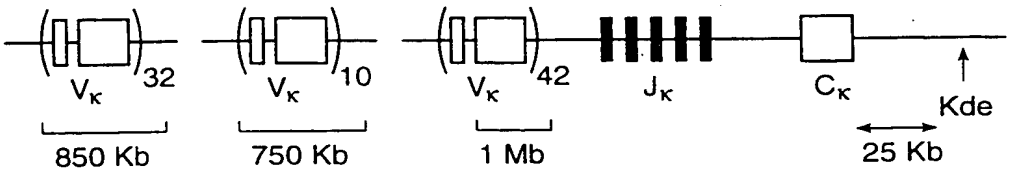


FIG. 3

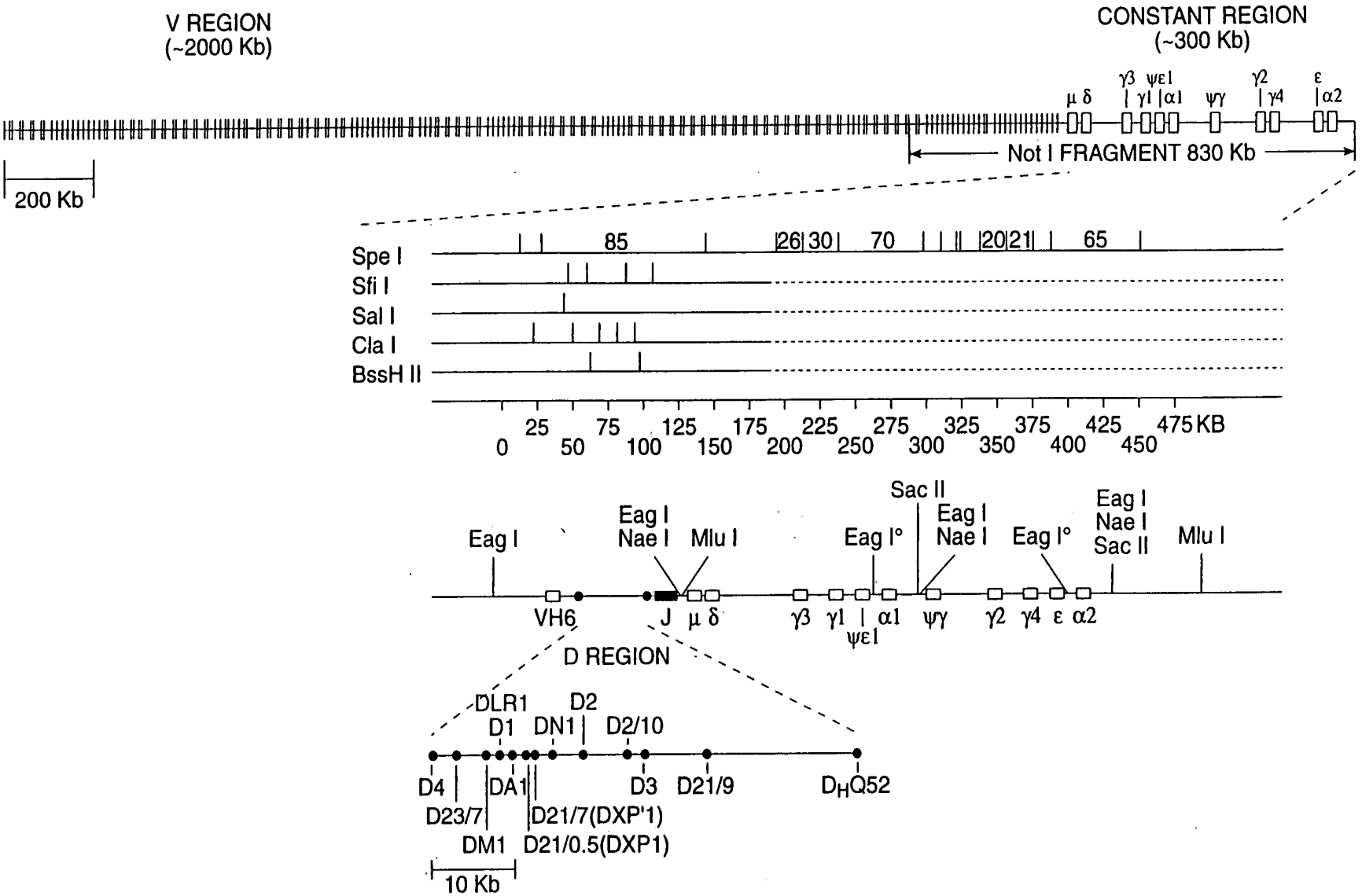

V REGION
(~2000 Kb)
CONSTANT REGION
(~300 Kb)
μ δ
γ3 ψε1 γ1 α1
ψγ
γ2 γ4
ε α2
Not I FRAGMENT 830 Kb
200 Kb
Spe I
Sfi I
Sal I
Cla I
BssH II
85
26 30
70
20 21
65
0 25 50 75 100 125 150 175 200 225 250 275 300 325 350 375 400 425 450 475 KB
Eag I
Eag I
Nae I
Mlu I
Eag I°
Sac II
Eag I
Nae I
Eag I°
Eag I
Nae I
Sac II
Mlu I
VH6
J μ δ
γ3 γ1 ψε1 α1 ψγ γ2 γ4 ε α2
D REGION
DLR1
D1
DN1
D2
D2/10
D4
D23/7
DM1
DA1
D21/7(DXP'1)
D21/0.5(DXP1)
D3
D21/9
DHQ52
10 Kb

FIG. 4

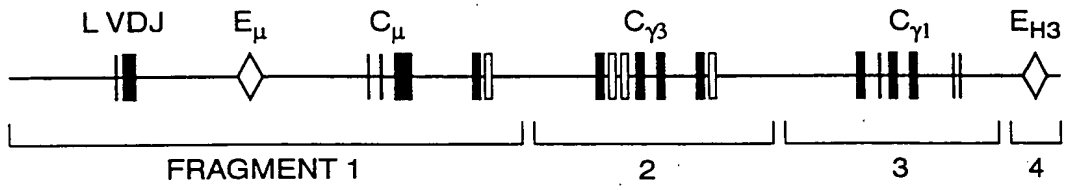

L VDJ
E_μ
C_μ
$C_{\gamma 3}$
$C_{\gamma 1}$
E_{H3}
FRAGMENT 1
2
3
4

FIG. 5

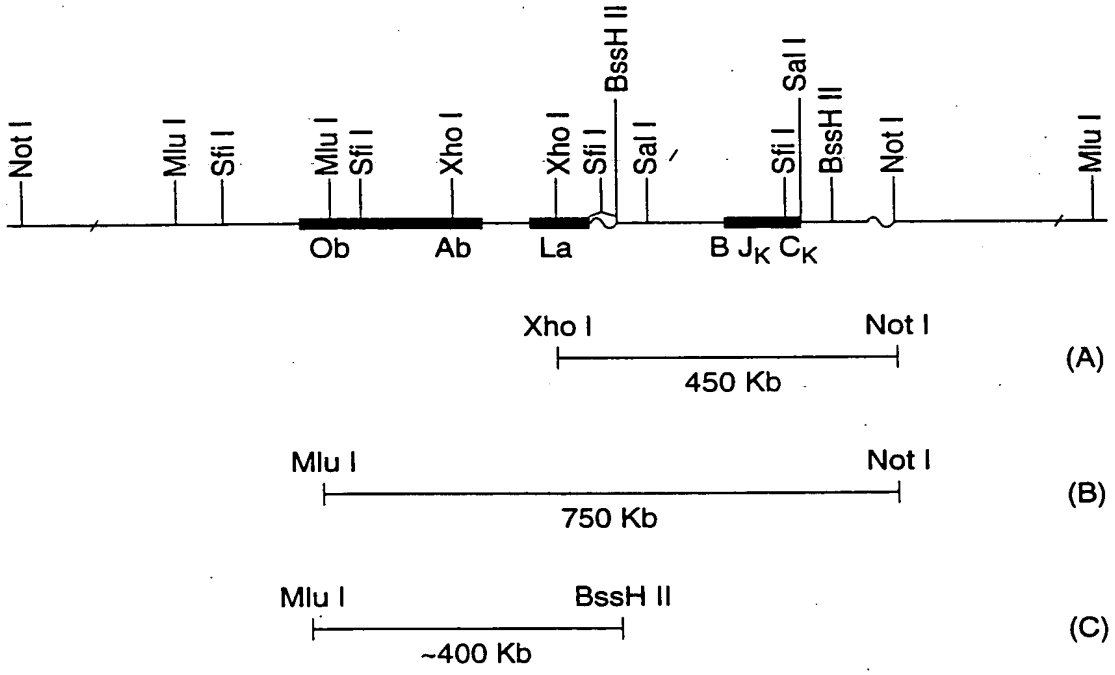

Not I
Mlu I
Sfi I
Mlu I
Sfi I
Xho I
Xho I
Sfi I
BssH II
Sal I
Sal I
Sfi I
BssH II
Not I
Mlu I
Ob
Ab
La
B J_K C_K
Xho I
Not I
450 Kb
(A)
Mlu I
Not I
750 Kb
(B)
Mlu I
BssH II
~400 Kb
(C)

FIG. 6

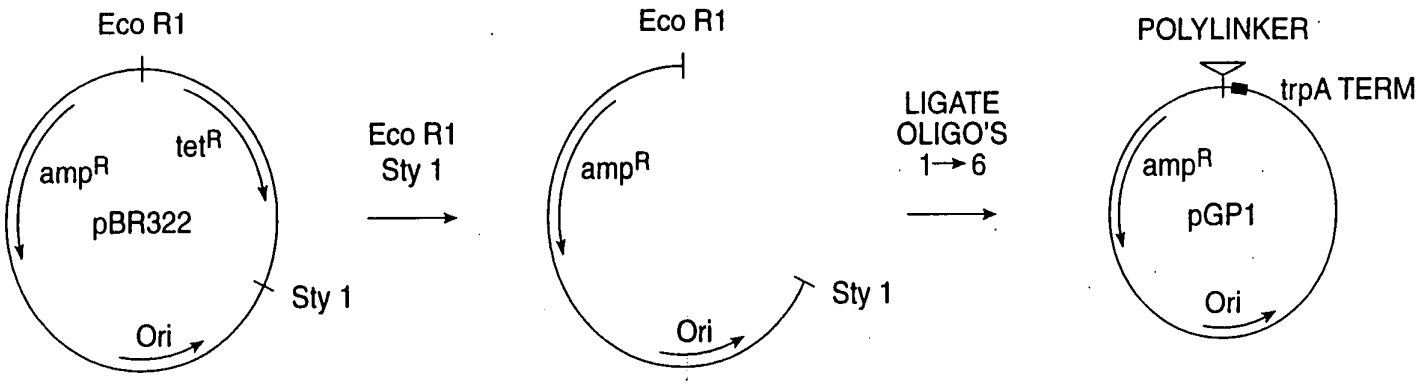
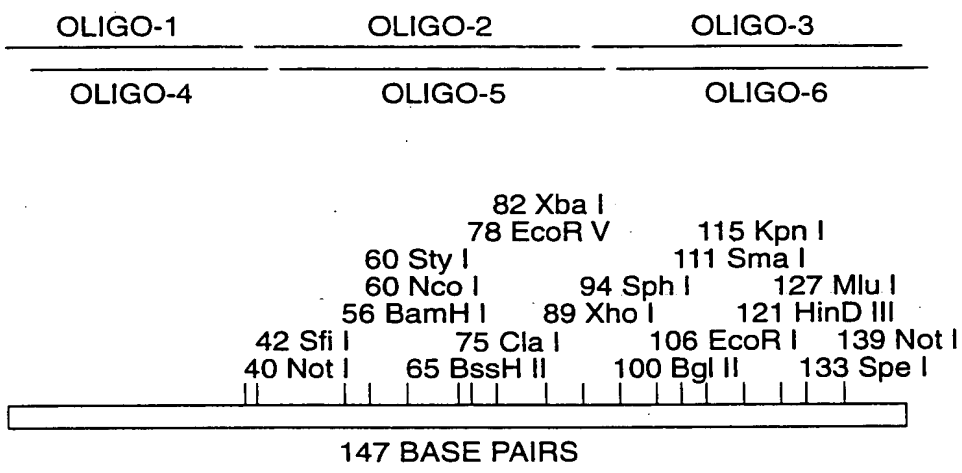
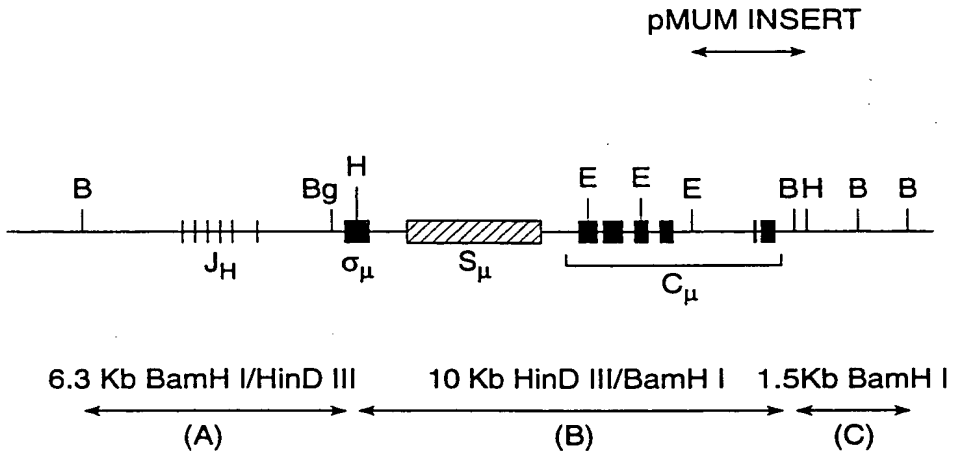

Eco R1
amp^R
tet^R
pBR322
Sty 1
Ori
Eco R1
Sty 1
Eco R1
amp^R
Sty 1
Ori
LIGATE
OLIGO'S
1→6
POLYLINKER
trpA TERM
amp^R
pGP1
Ori

FIG. 7



pGP1 POLYLINKER

FIG. 8



HUMAN μ LOCUS

FIG. 9

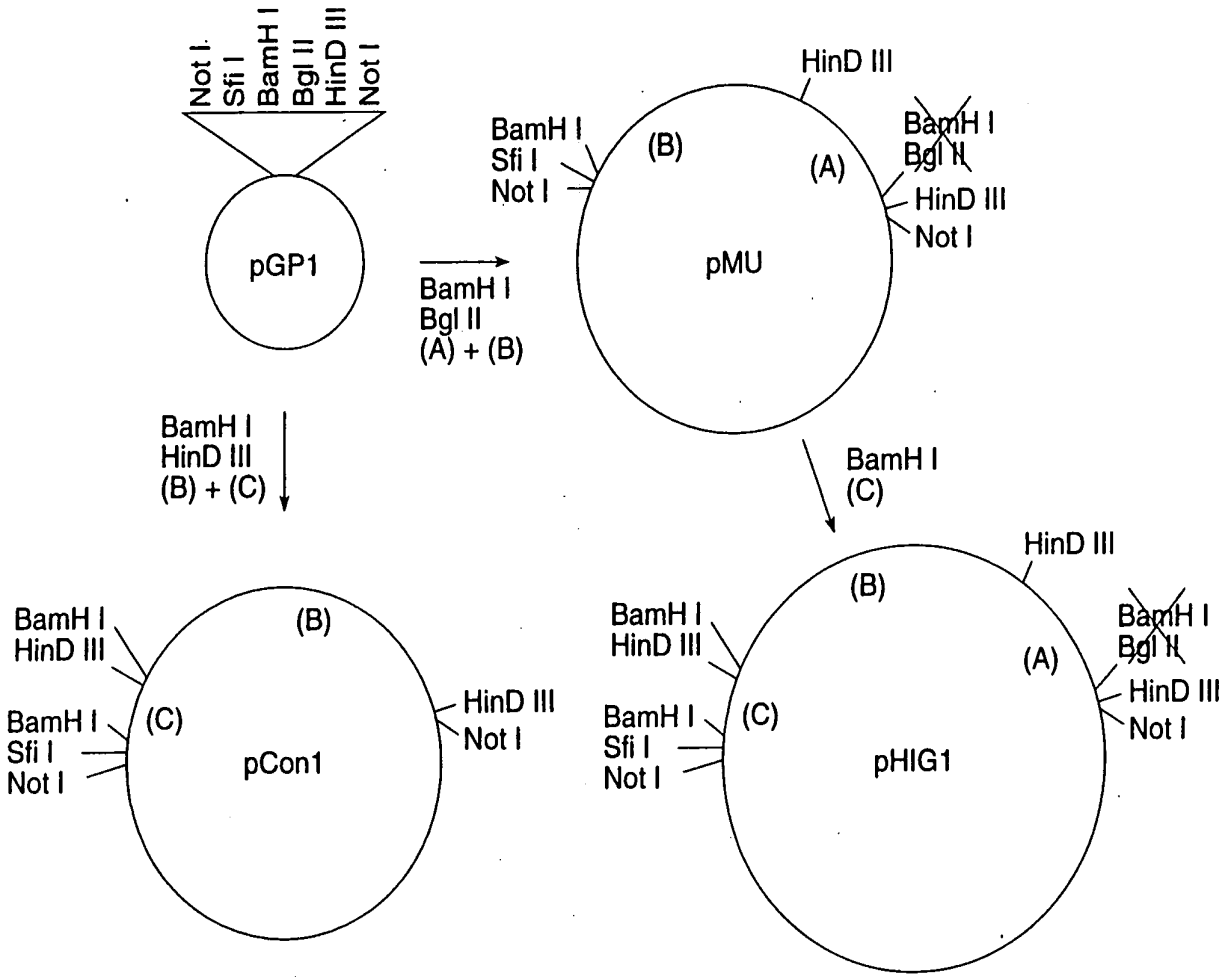

Not I
Sfi I
BamH I
Bgl II
HinD III
Not I
pGP1
BamH I
Bgl II
(A) + (B)
HinD III
BamH I
Sfi I
Not I
(B)
(A)
BamH I
Bgl II
HinD III
Not I
pMU
BamH I
HinD III
(B) + (C)
BamH I
(C)
BamH I
HinD III
(B)
HinD III
BamH I
Sfi I
Not I
(C)
pCon1
Not I
HinD III
(B)
BamH I
HinD III
BamH I
Bgl II
(A)
HinD III
Not I
BamH I
Sfi I
Not I
(C)
pHIG1

FIG. 10

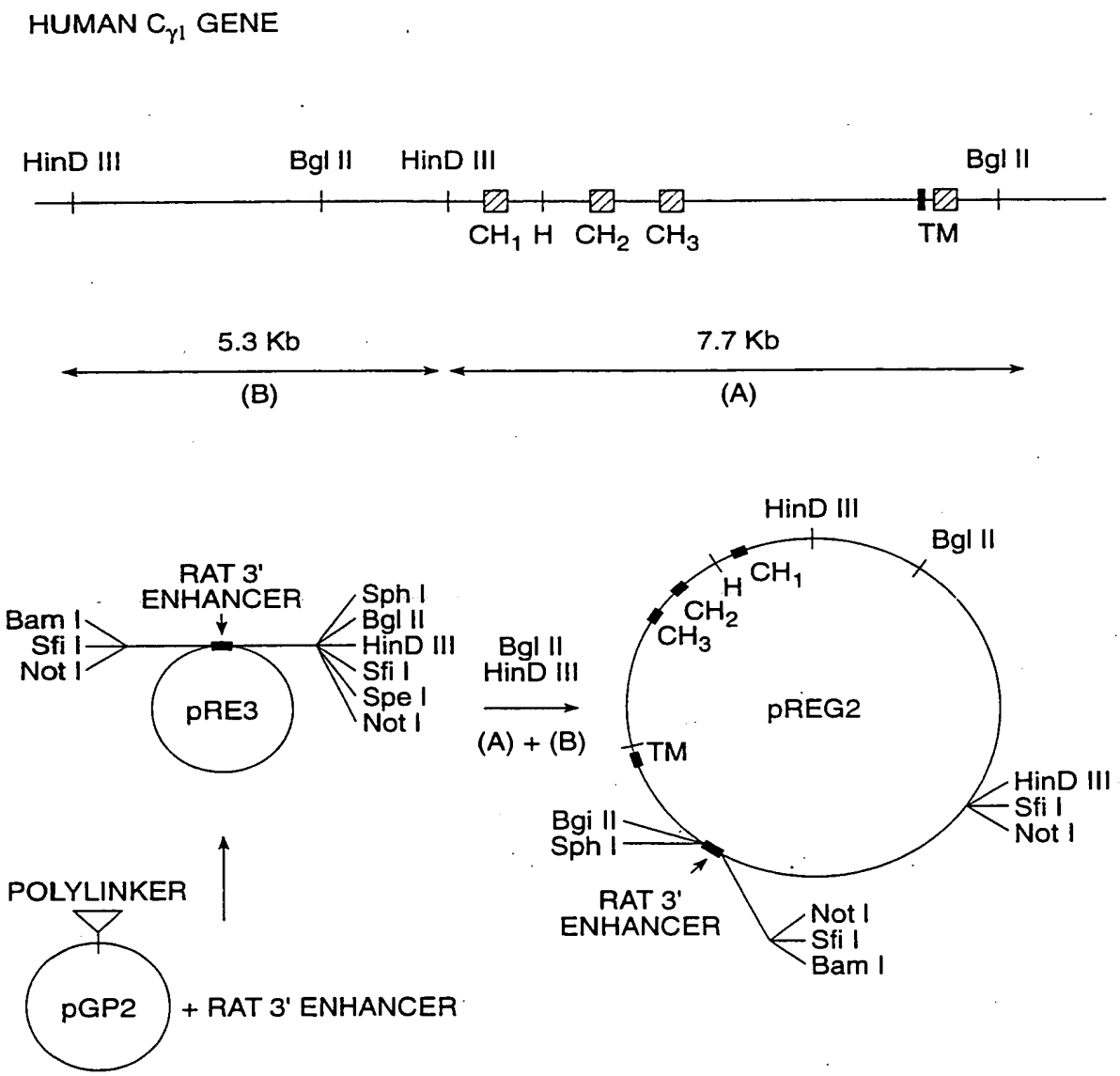
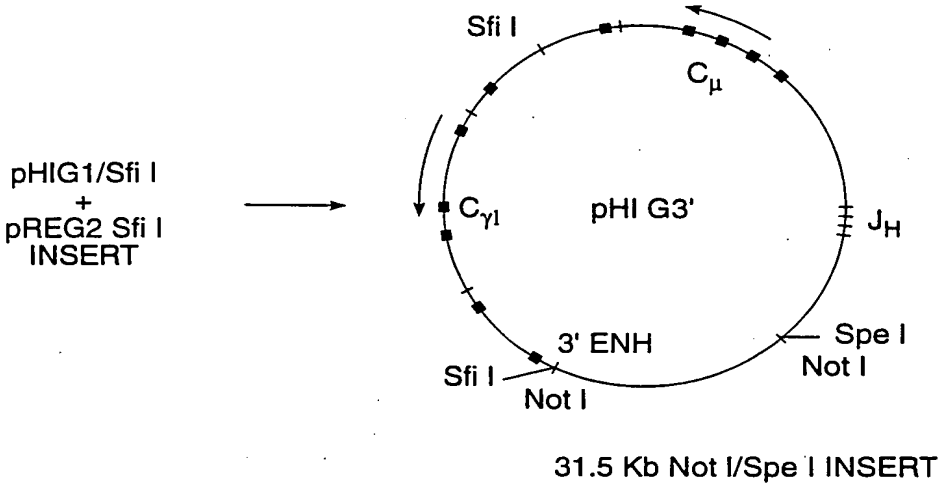

HUMAN $C_{\gamma 1}$ GENE
HinD III
Bgl II
HinD III
Bgl II
CH_1 H CH_2 CH_3
TM
5.3 Kb
(B)
7.7 Kb
(A)
RAT 3' ENHANCER
Bam I
Sfi I
Not I
pRE3
Sph I
Bgl II
HinD III
Sfi I
Spe I
Not I
Bgl II
HinD III
(A) + (B)
HinD III
Bgl II
CH_1
H
CH_2
CH_3
pREG2
TM
HinD III
Sfi I
Not I
Bgi II
Sph I
RAT 3' ENHANCER
Not I
Sfi I
Bam I
POLYLINKER
pGP2
+ RAT 3' ENHANCER

FIG. 11


pHIG1/Sfi I
+
pREG2 Sfi I
INSERT
Sfi I
C_μ
$C_{\gamma 1}$
pHI G3'
J_H
3' ENH
Sfi I
Not I
Spe I
Not I
31.5 Kb Not I/Spe I INSERT

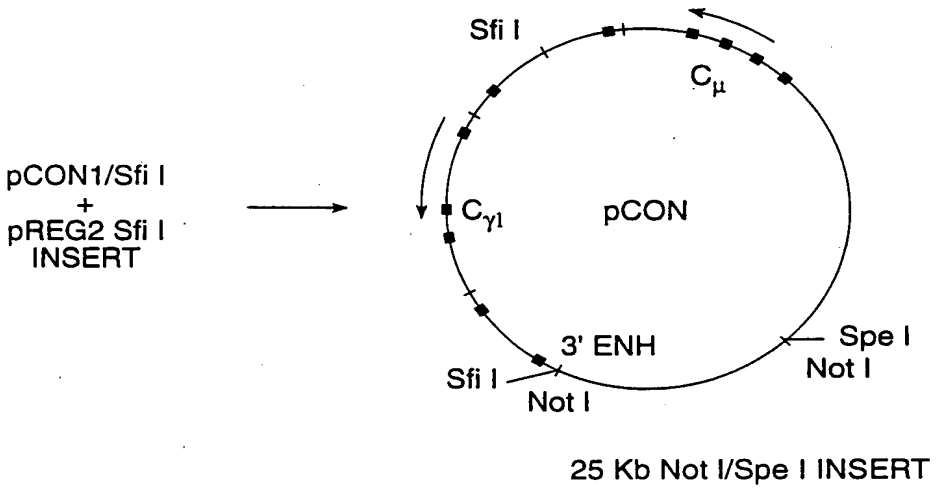

pCON1/Sfi I
+
pREG2 Sfi I
INSERT
Sfi I
C_μ
$C_{\gamma 1}$
pCON
3' ENH
Sfi I
Not I
Spe I
Not I
25 Kb Not I/Spe I INSERT

FIG. 12

HUMAN D REGION

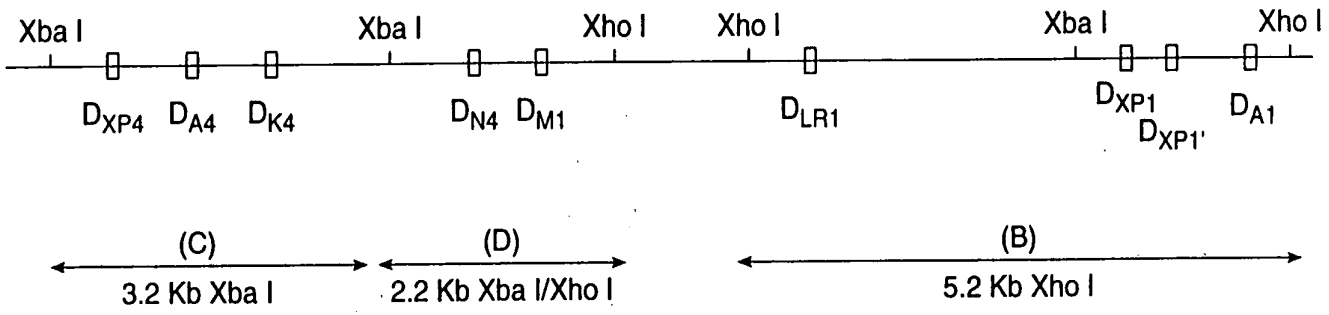


FIG. 13

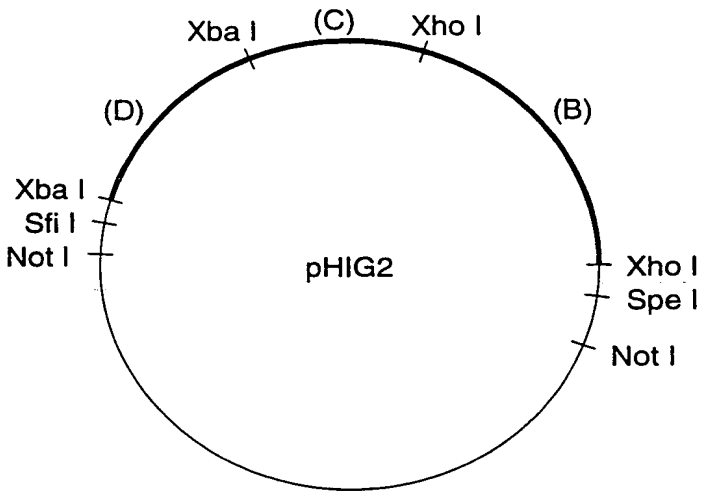


FIG. 14

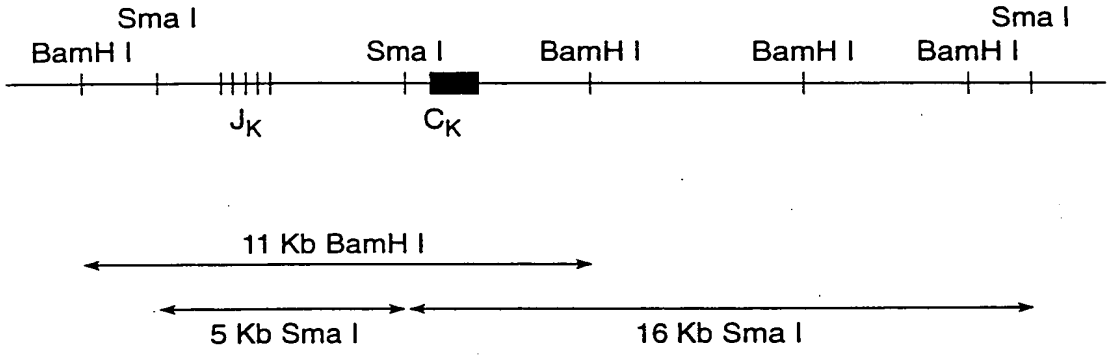

Sma I
BamH I
Sma I
BamH I
BamH I
Sma I
J_K
C_K
11 Kb BamH I
5 Kb Sma I
16 Kb Sma I

FIG. 15

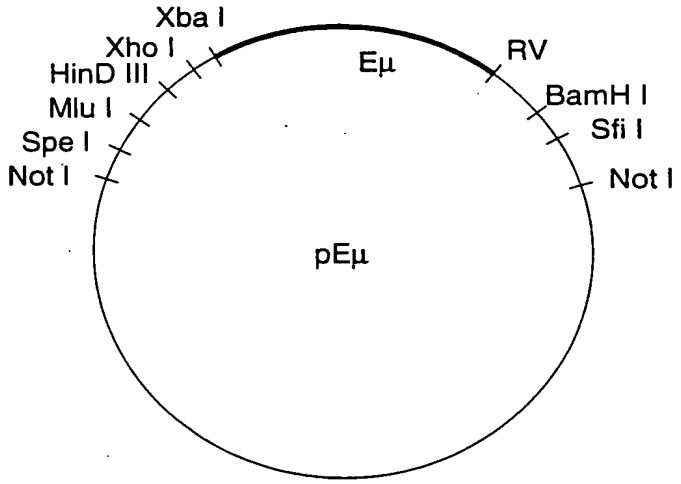

Xba I
Xho I
HinD III
Mlu I
Spe I
Not I
Eμ
RV
BamH I
Sfi I
Not I
pEμ

FIG. 16

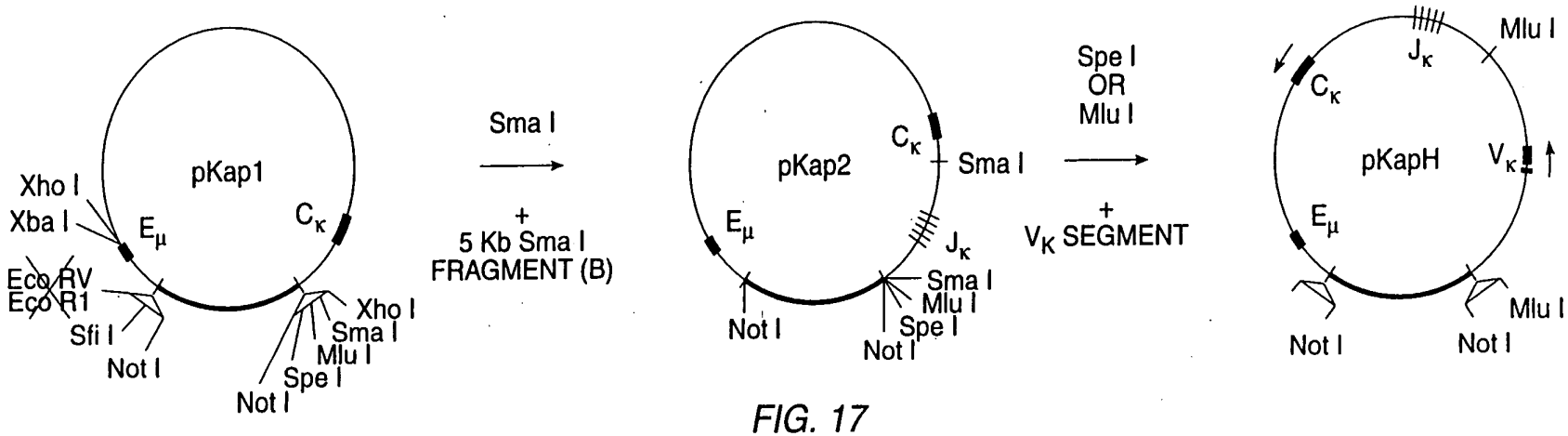

pKap1
Xho I
Xba I
Eμ
Cκ
Eco RV
Eco R1
Sfi I
Not I
Not I
Spe I
Mlu I
Sma I
Xho I
Sma I
+
5 Kb Sma I
FRAGMENT (B)
pKap2
Cκ
Sma I
Eμ
Jκ
Sma I
Mlu I
Not I
Spe I
Not I
Spe I
OR
Mlu I
+
VK SEGMENT
Mlu I
Jκ
Cκ
pKapH
Vκ
Eμ
Mlu I
Not I
Not I

FIG. 17

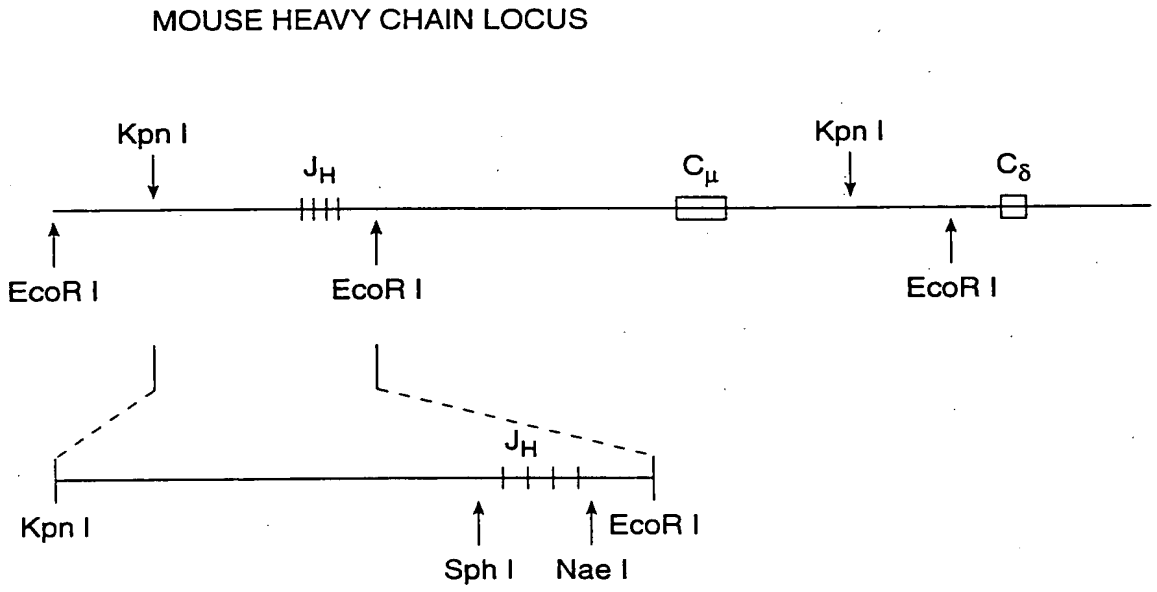

MOUSE HEAVY CHAIN LOCUS
Kpn I
J_H
C_μ
Kpn I
C_δ
EcoR I
EcoR I
EcoR I
J_H
Kpn I
Sph I
Nae I
EcoR I

FIG. 18A

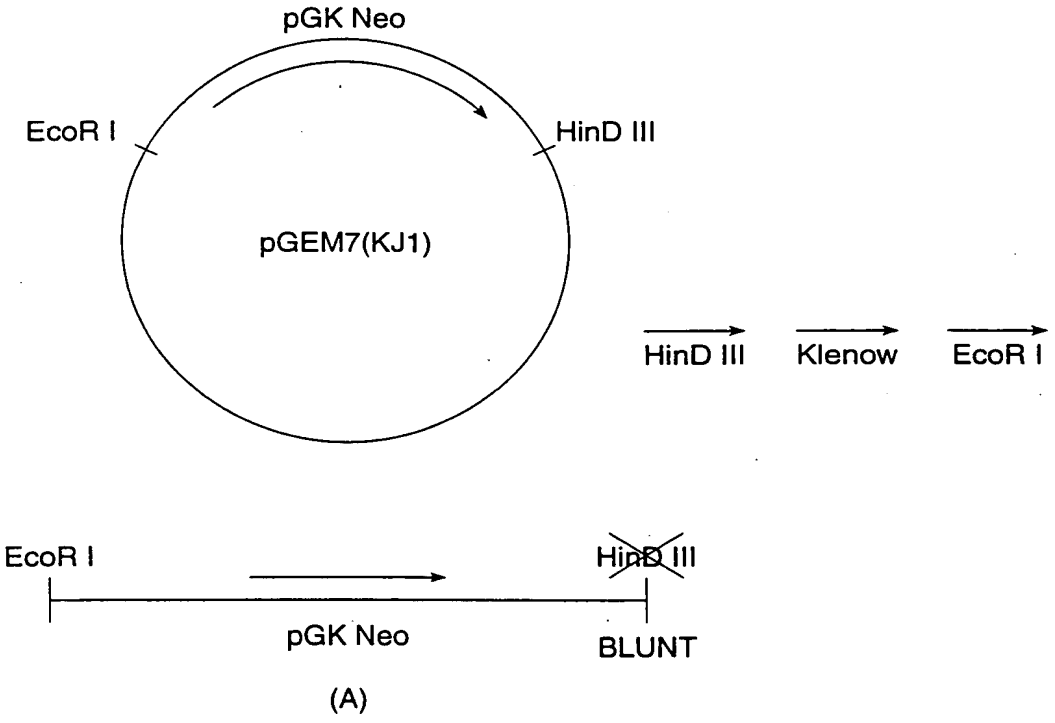

pGK Neo
EcoR I
HinD III
pGEM7(KJ1)
HinD III
Klenow
EcoR I
EcoR I
HinD III
pGK Neo
BLUNT
(A)

FIG. 18B

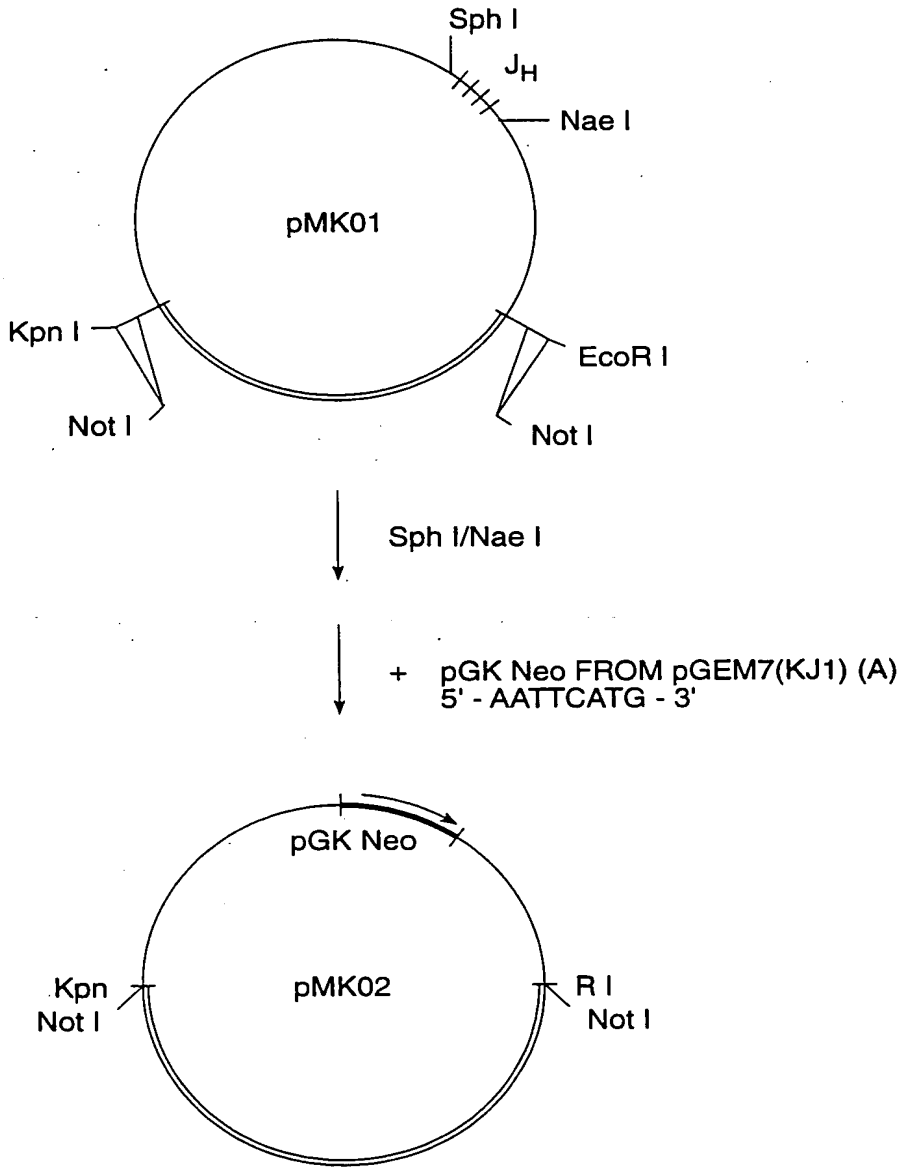

Sph I
J_H
Nae I
pMK01
Kpn I
EcoR I
Not I
Not I
Sph I/Nae I
+ pGK Neo FROM pGEM7(KJ1) (A)
5' - AATTCATG - 3'
pGK Neo
Kpn
Not I
pMK02
R I
Not I

FIG. 18C

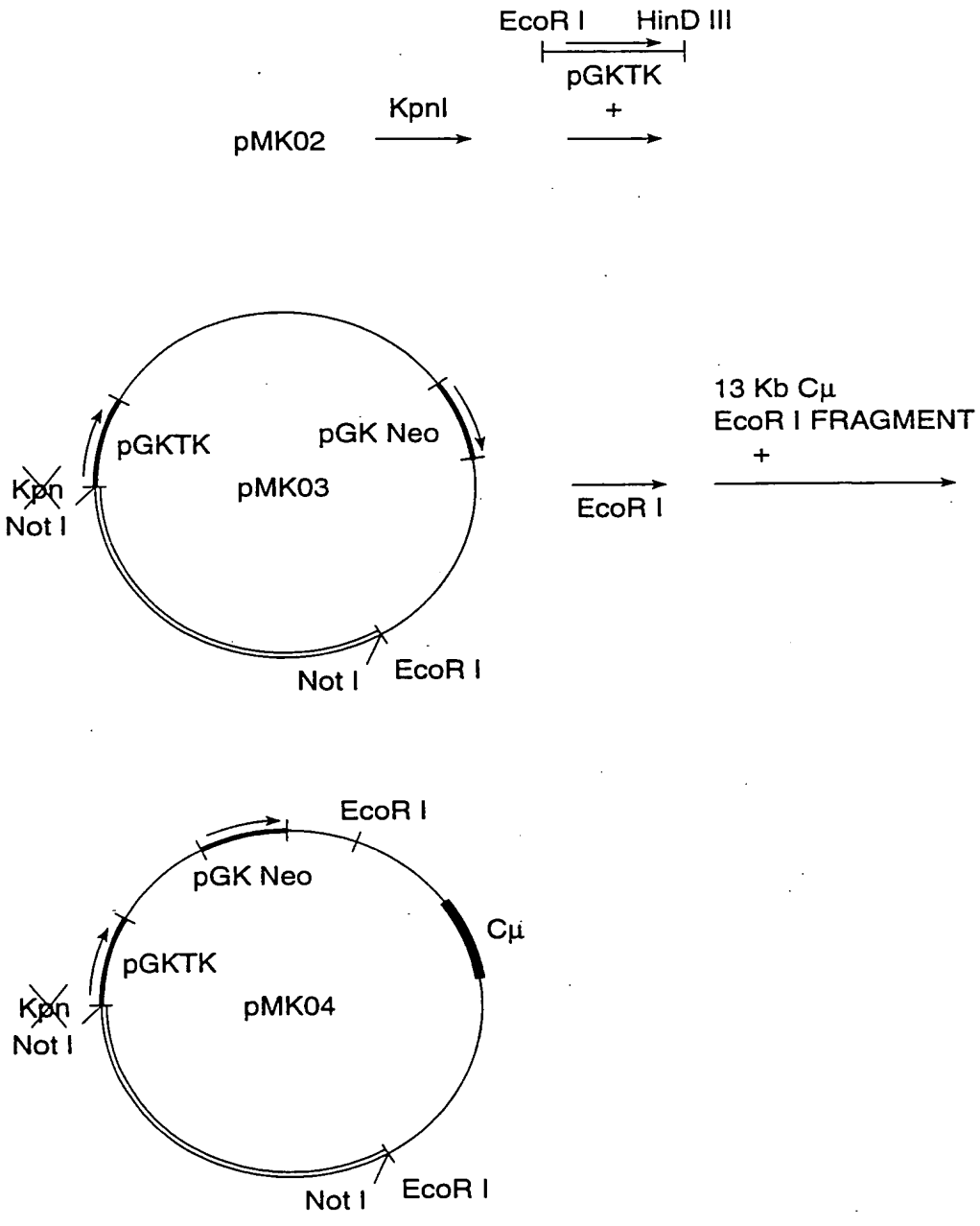

EcoR I
HinD III
pGKTK
+
KpnI
pMK02
pGKTK
pGK Neo
pMK03
Kpn
Not I
Not I
EcoR I
13 Kb Cμ
EcoR I FRAGMENT
+
EcoR I
EcoR I
pGK Neo
Cμ
pGKTK
pMK04
Kpn
Not I
Not I
EcoR I

FIG. 18D

MOUSE KAPPA GENE

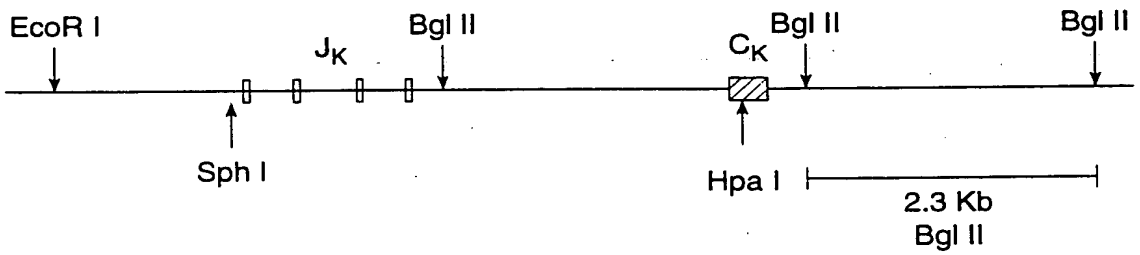


FIG. 19A

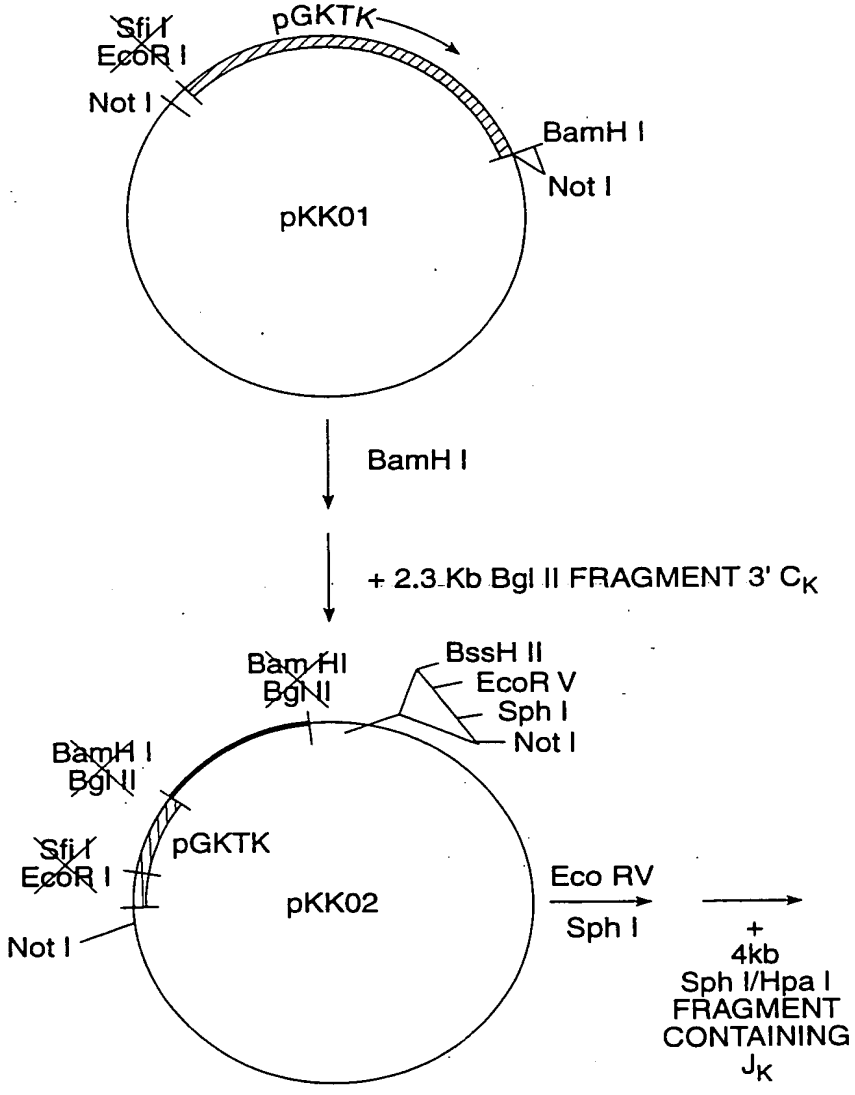

Sfi I
EcoR I
pGKTK
Not I
BamH I
Not I
pKK01
BamH I
+ 2.3 Kb Bgl II FRAGMENT 3' C_K
Bam HI
BgNI
BssH II
EcoR V
Sph I
Not I
BamH I
BgNI
Sfi I
EcoR I
pGKTK
pKK02
Not I
Eco RV
Sph I
+
4kb
Sph I/Hpa I
FRAGMENT
CONTAINING
J_K

FIG. 19B

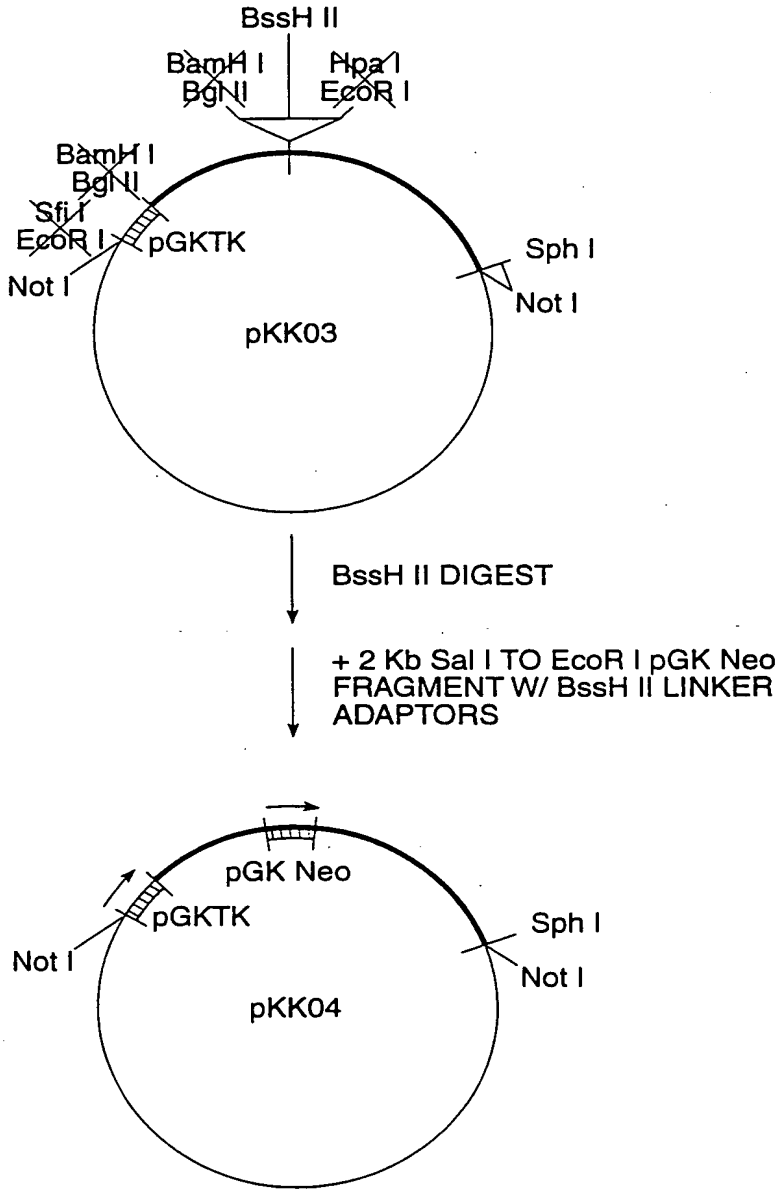

BssH II
BamH I
BglII
Hpa I
EcoR I
BamH I
BglII
Sfi I
EcoR I
pGKTK
Not I
Sph I
Not I
pKK03
BssH II DIGEST
+ 2 Kb Sal I TO EcoR I pGK Neo
FRAGMENT W/ BssH II LINKER
ADAPTORS
pGK Neo
pGKTK
Not I
Sph I
Not I
pKK04

FIG. 19C

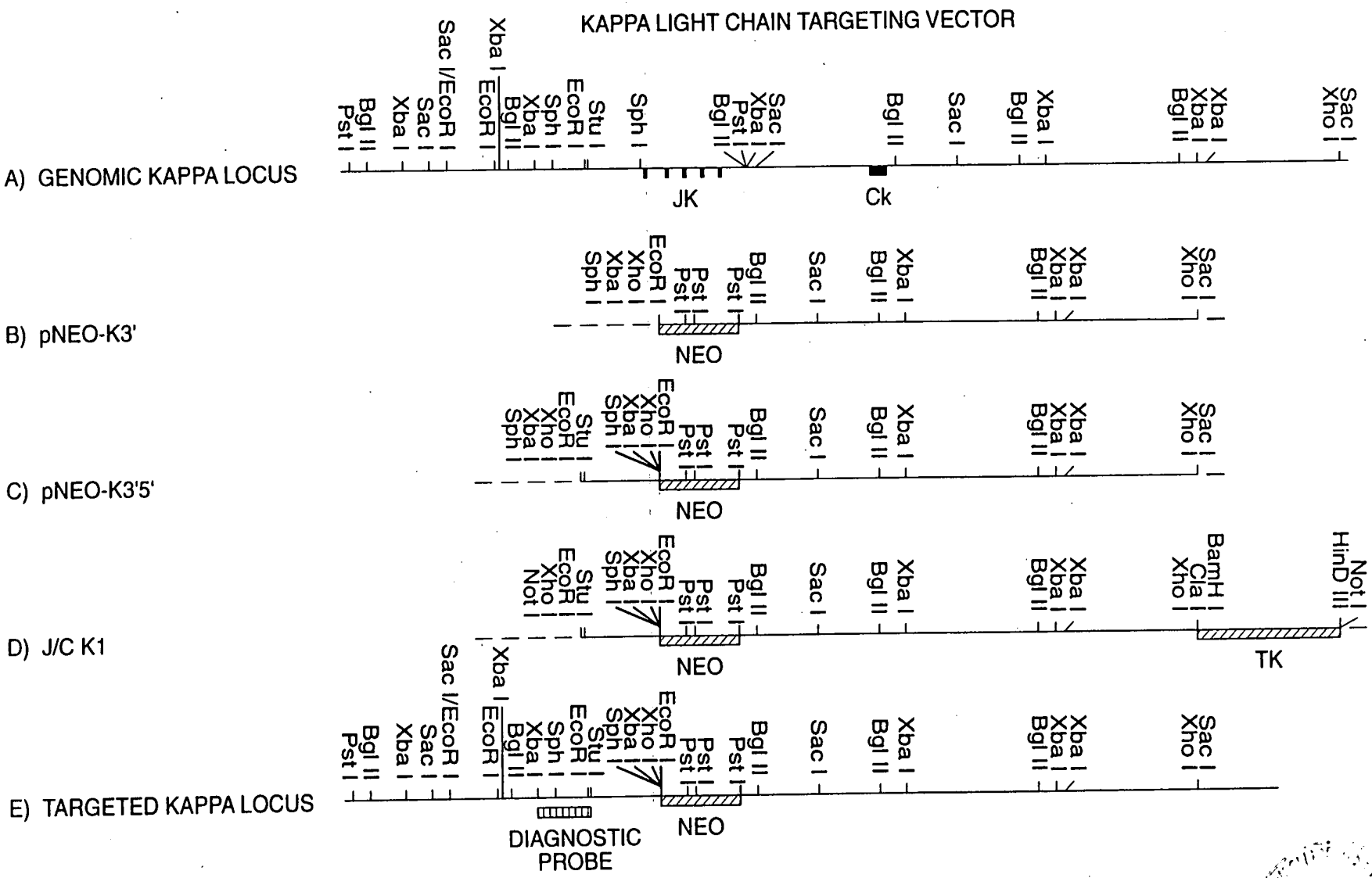

KAPPA LIGHT CHAIN TARGETING VECTOR
A) GENOMIC KAPPA LOCUS
B) pNEO-K3'
C) pNEO-K3'5'
D) J/C K1
E) TARGETED KAPPA LOCUS
JK
Ck
NEO
TK
DIAGNOSTIC PROBE

FIG. 20

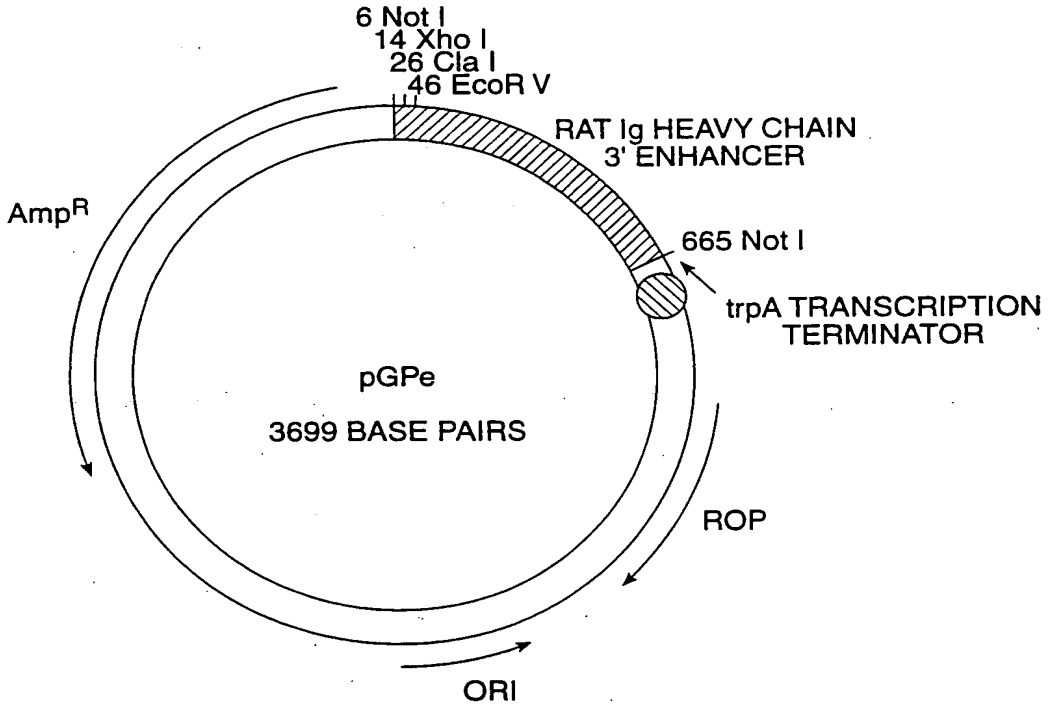

6 Not I
14 Xho I
26 Cla I
46 EcoR V
RAT Ig HEAVY CHAIN
3' ENHANCER
AmpR
665 Not I
trpA TRANSCRIPTION
TERMINATOR
pGPe
3699 BASE PAIRS
ROP
ORI

FIG. 22

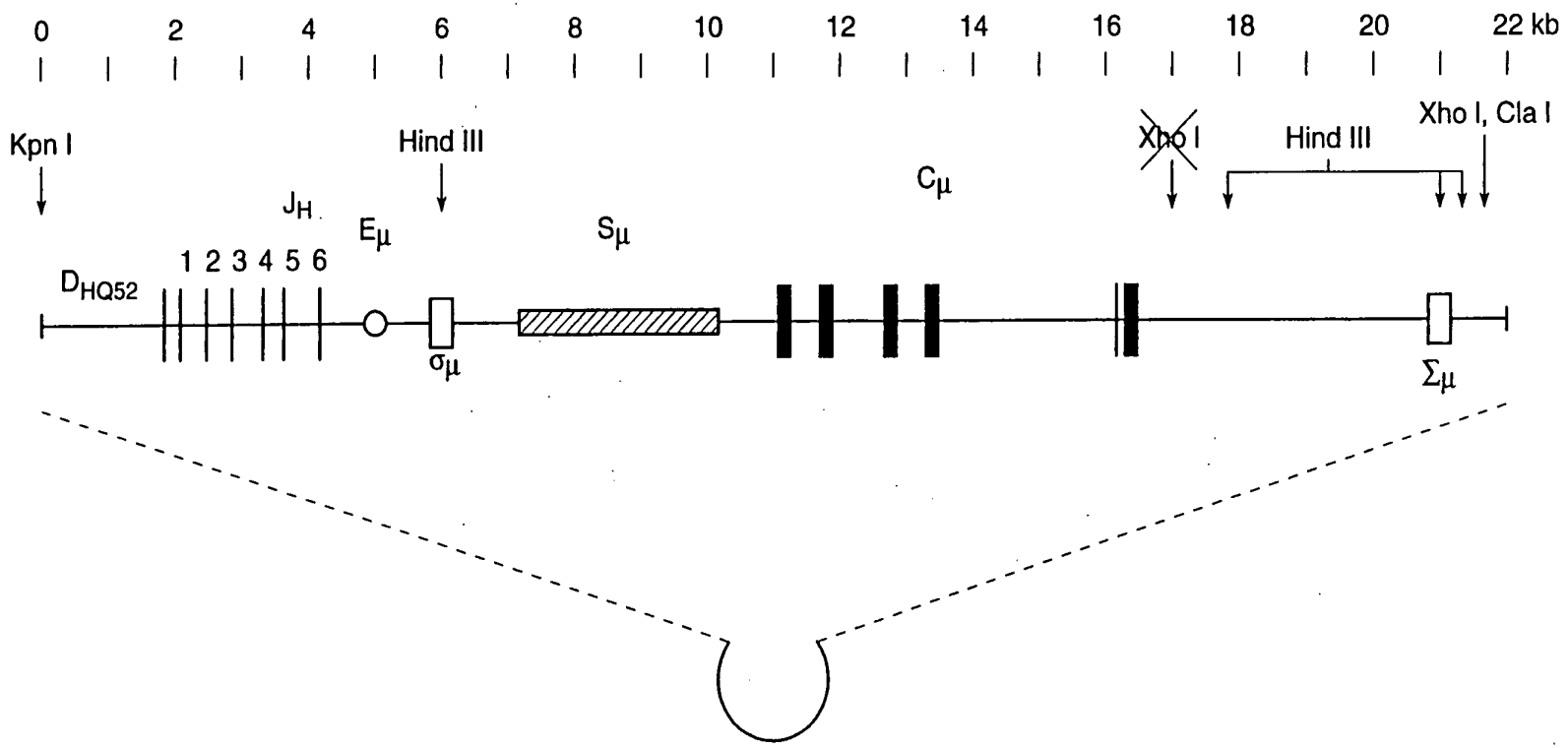

0
2
4
6
8
10
12
14
16
18
20
22 kb
Kpn I
Hind III
Xho I
Hind III
Xho I, Cla I
J_H
$E\mu$
$C\mu$
$S\mu$
1 2 3 4 5 6
D_{HQ52}
$\sigma\mu$
$\Sigma\mu$

FIG. 23

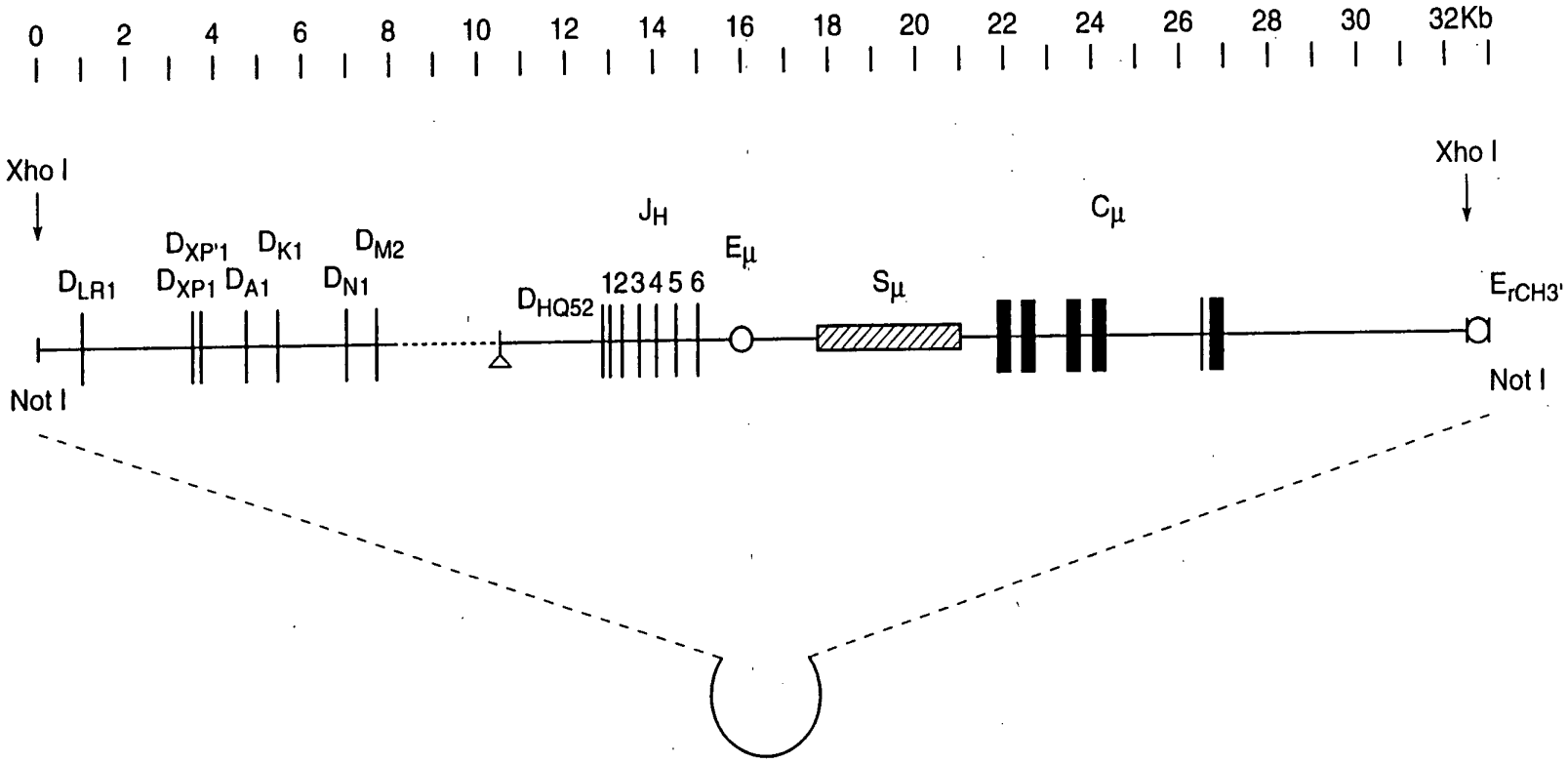

0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32Kb
Xho I
Xho I
J_H
C_μ
E_μ
$D_{XP'1}$
D_{K1}
D_{M2}
D_{LR1}
D_{XP1}
D_{A1}
D_{N1}
D_{HQ52}
1 2 3 4 5 6
S_μ
$E_{rCH3'}$
Not I
Not I

FIG. 24

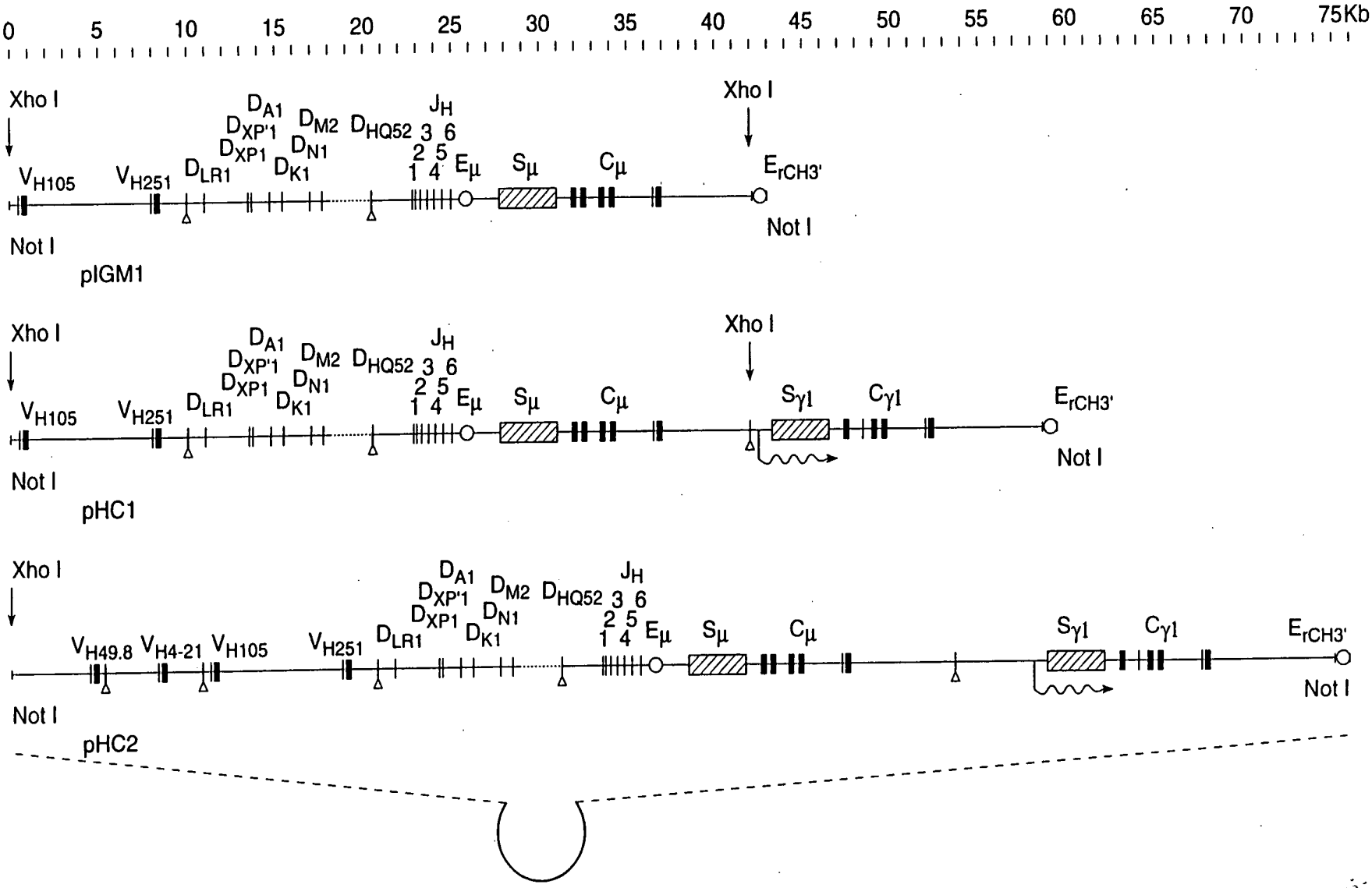

0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75Kb
Xho I
Not I
pIGM1
pHC1
pHC2
V_{H105}
V_{H251}
$V_{H49.8}$
V_{H4-21}
D_{LR1}
D_{K1}
D_{XP1}
$D_{XP'1}$
D_{N1}
D_{M2}
D_{A1}
D_{HQ52}
J_H 1 2 3 4 5 6
E_μ
S_μ
C_μ
$S_{\gamma 1}$
$C_{\gamma 1}$
$E_{rCH3'}$

FIG. 25

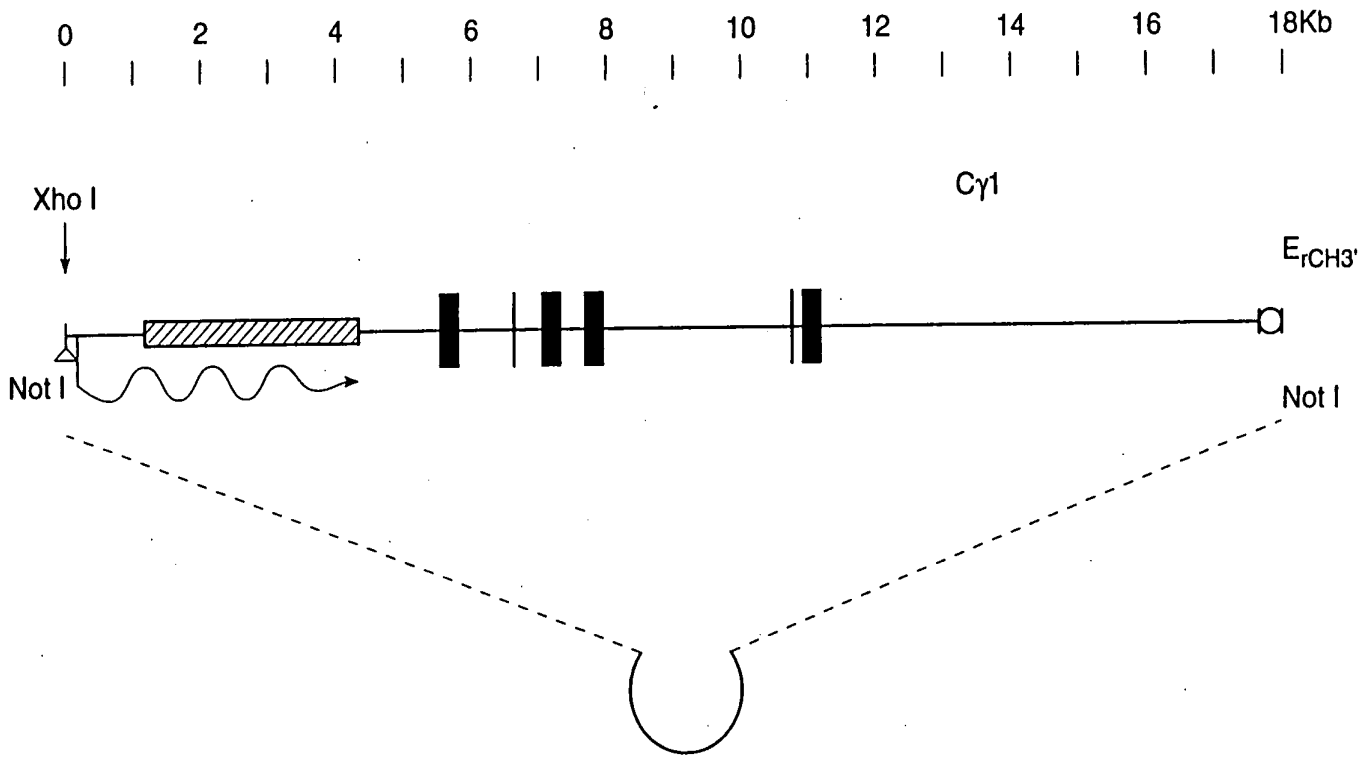


FIG. 26

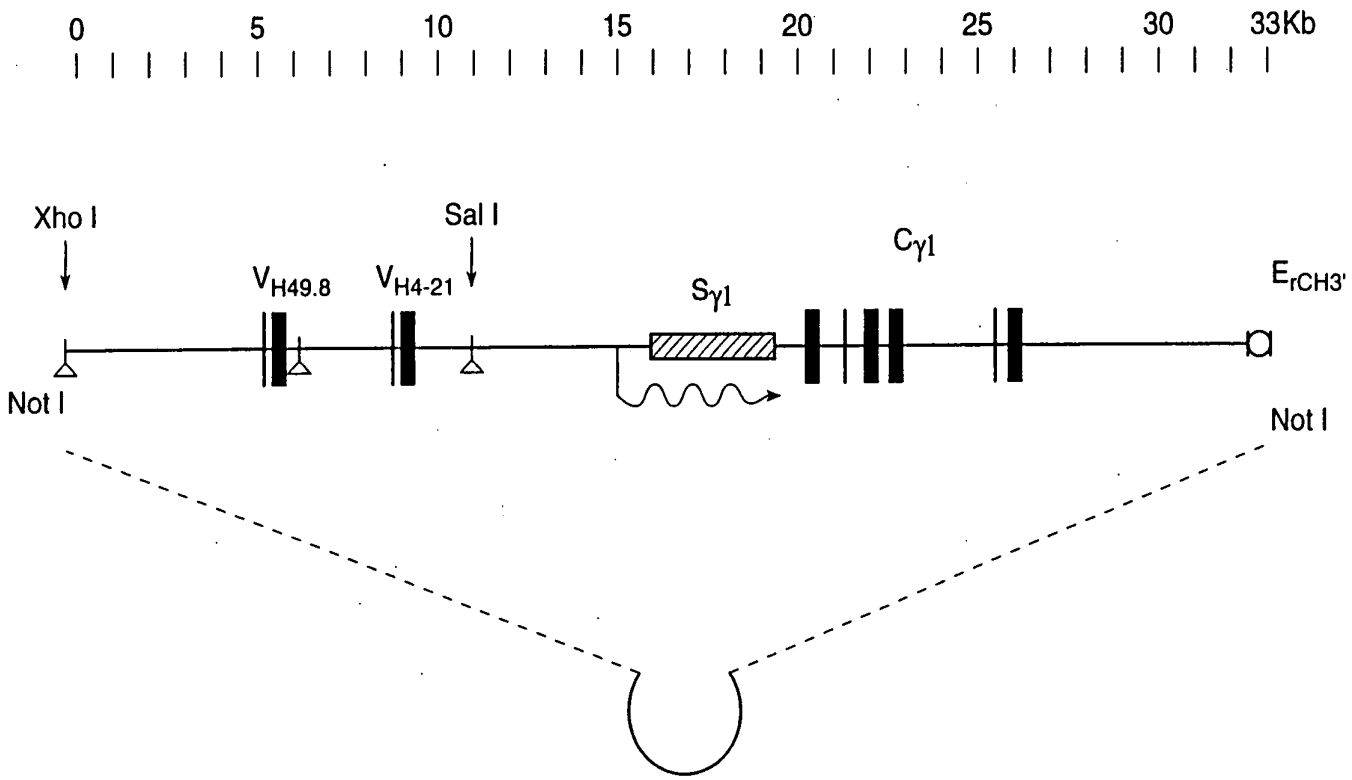

0
5
10
15
20
25
30
33Kb
Xho I
Sal I
$C_{\gamma 1}$
$E_{rCH3'}$
$V_{H49.8}$
V_{H4-21}
$S_{\gamma 1}$
Not I
Not I

FIG. 27

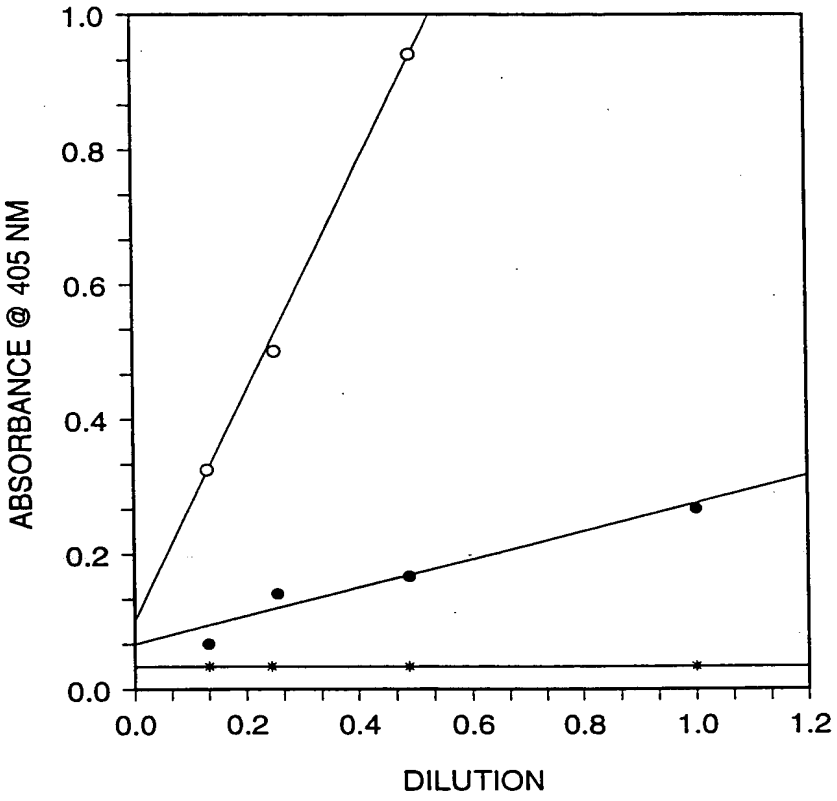

1.0
0.8
0.6
0.4
0.2
0.0
ABSORBANCE @ 405 NM
0.0
0.2
0.4
0.6
0.8
1.0
1.2
DILUTION
IgM
IgG1
pHC1 TRANSGENIC
IgM
IgG1
NON-TRANSGENIC CONTROL

FIG. 28

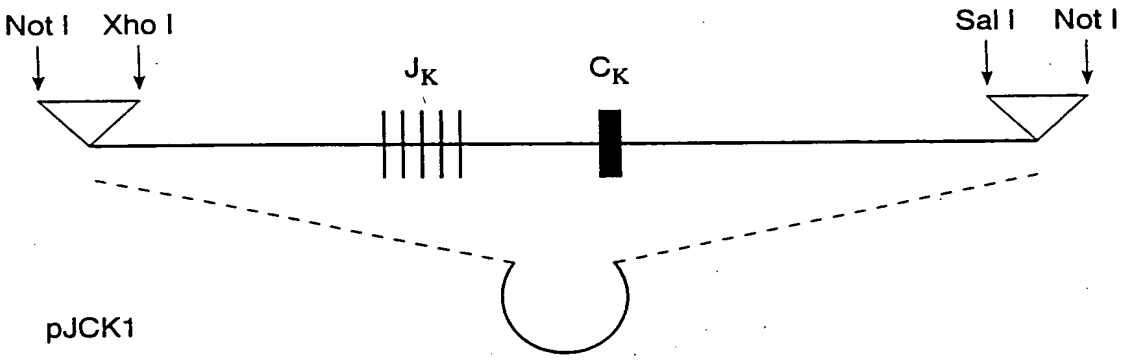


FIG. 29

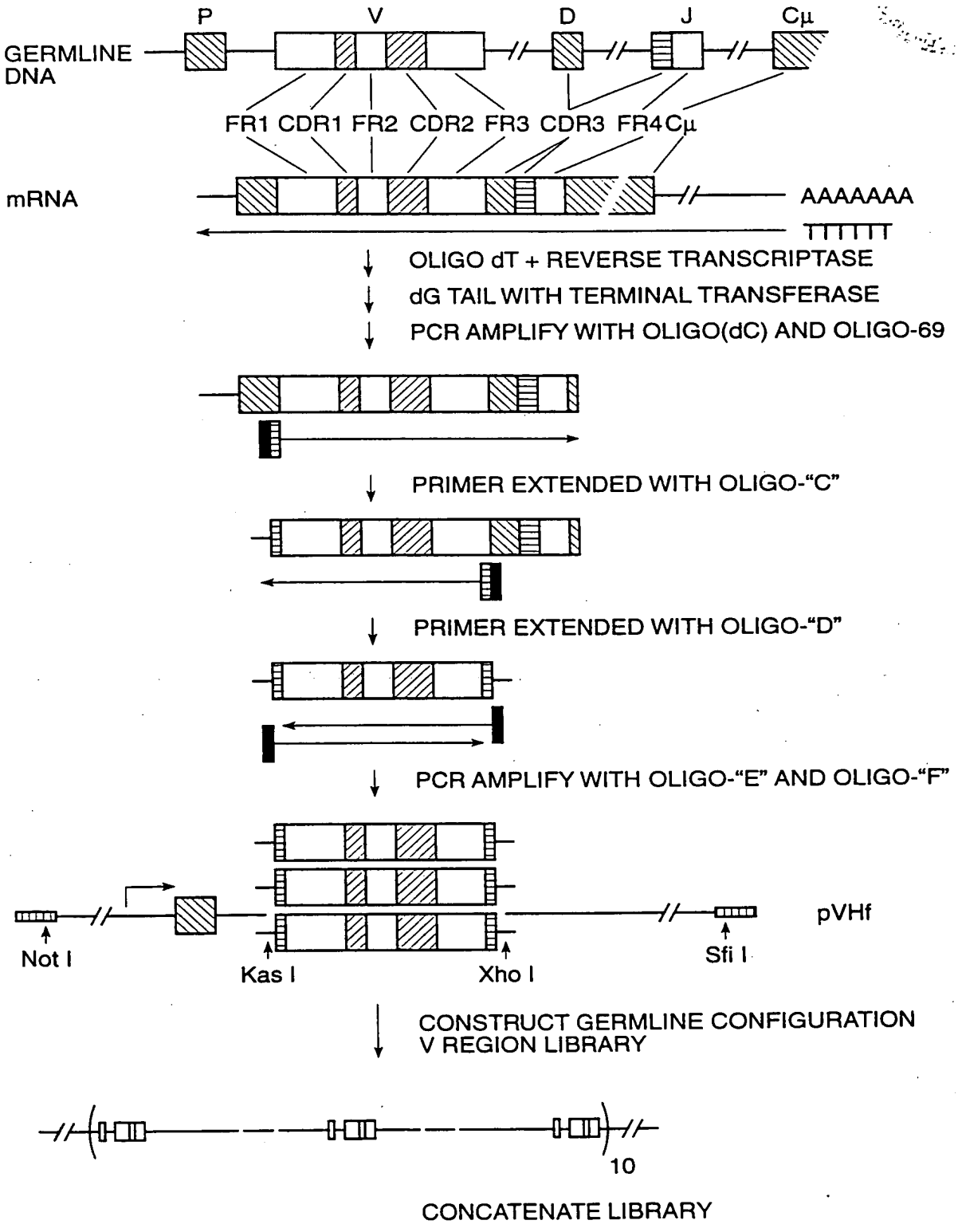

P
V
D
J
Cμ
GERMLINE DNA
FR1 CDR1 FR2 CDR2 FR3 CDR3 FR4Cμ
mRNA
AAAAAAA
TTTTTT
OLIGO dT + REVERSE TRANSCRIPTASE
dG TAIL WITH TERMINAL TRANSFERASE
PCR AMPLIFY WITH OLIGO(dC) AND OLIGO-69
PRIMER EXTENDED WITH OLIGO-"C"
PRIMER EXTENDED WITH OLIGO-"D"
PCR AMPLIFY WITH OLIGO-"E" AND OLIGO-"F"
pVHf
Not I
Kas I
Xho I
Sfi I
CONSTRUCT GERMLINE CONFIGURATION
V REGION LIBRARY
10
CONCATENATE LIBRARY
SYNTHETIC HEAVY CHAIN VARIABLE REGION

FIG. 30

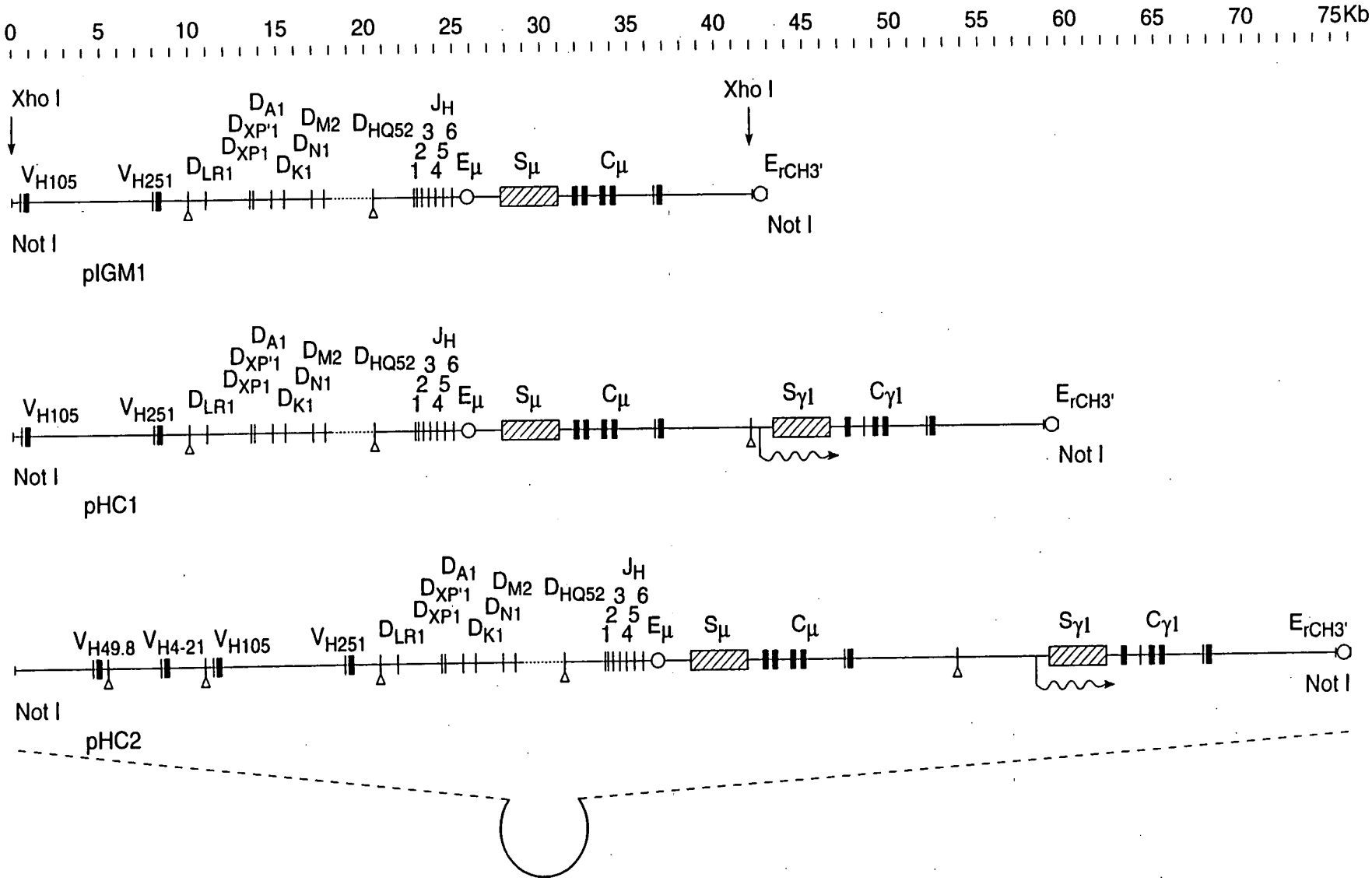

0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75Kb
Xho I
Xho I
D_{A1}
$D_{XP'1}$
D_{XP1}
D_{M2}
D_{N1}
D_{K1}
D_{HQ52}
J_H
2 3 6
1 4 5
V_{H105}
V_{H251}
D_{LR1}
E_μ
S_μ
C_μ
$E_{rCH3'}$
Not I
Not I
pIGM1
$S_{\gamma 1}$
$C_{\gamma 1}$
Not I
Not I
pHC1
$V_{H49.8}$
V_{H4-21}
Not I
Not I
pHC2

FIG. 31

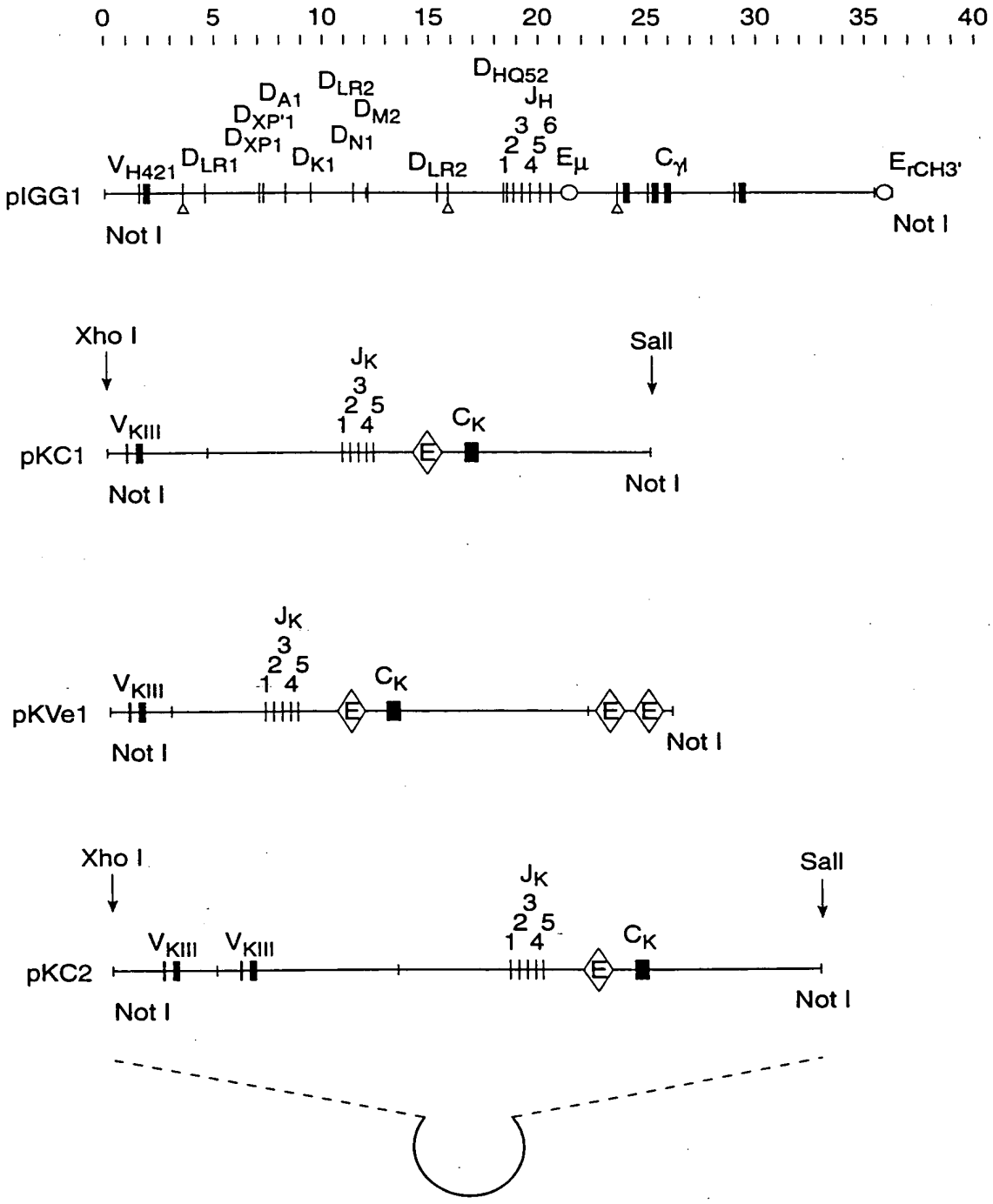

0
5
10
15
20
25
30
35
40
pIGG1
Not I
Not I
Xho I
Sall
pKC1
Not I
Not I
pKVe1
Not I
Not I
Xho I
Sall
pKC2
Not I
Not I

FIG. 32

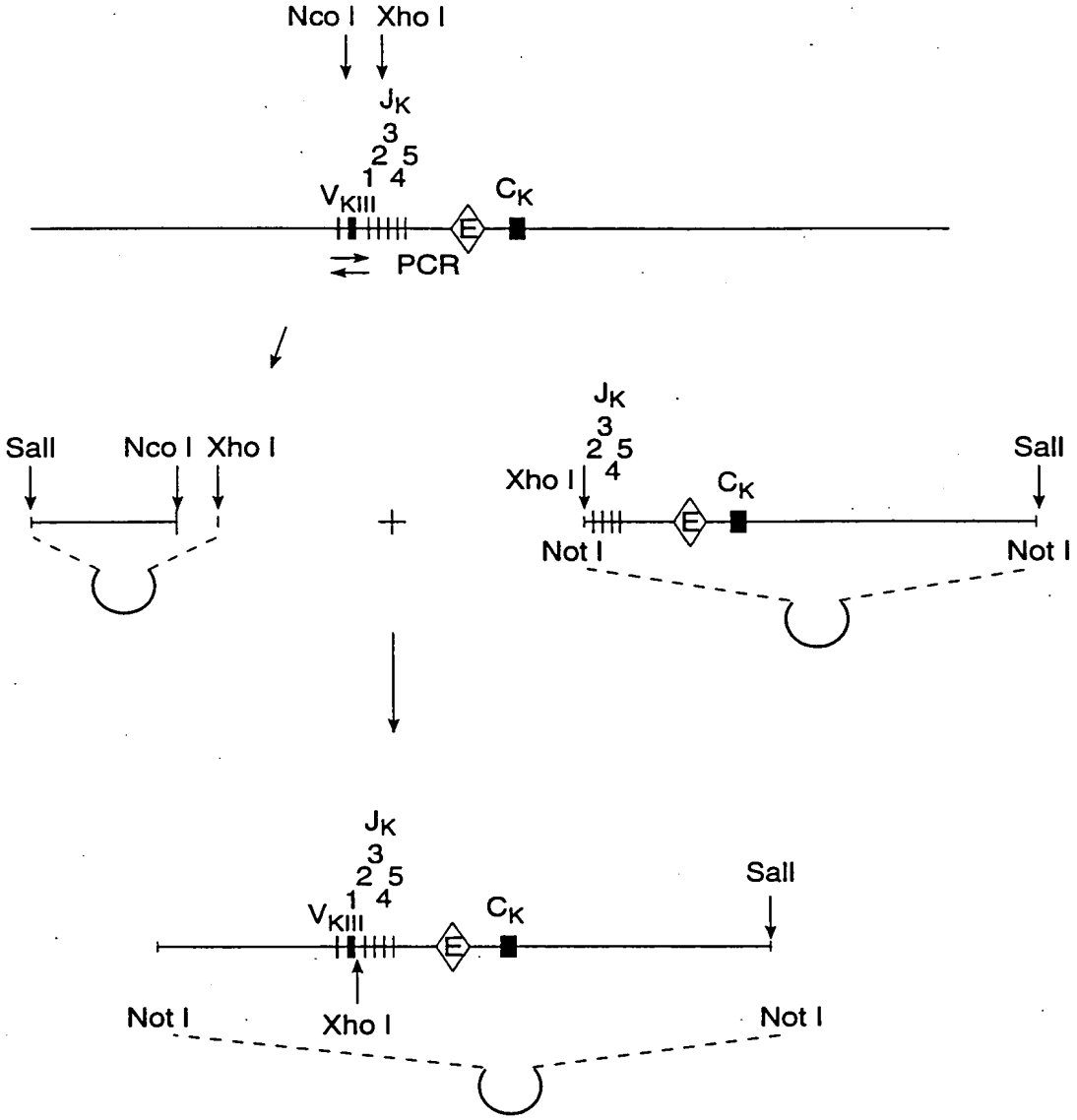

Nco I
Xho I
J_K
3
2
5
1
4
V_{KIII}
C_K
E
PCR
SalI
Nco I
Xho I
J_K
3
2
5
4
Xho I
C_K
E
SalI
Not I
Not I
J_K
3
2
5
1
4
V_{KIII}
C_K
E
SalI
Not I
Xho I
Not I

FIG. 33

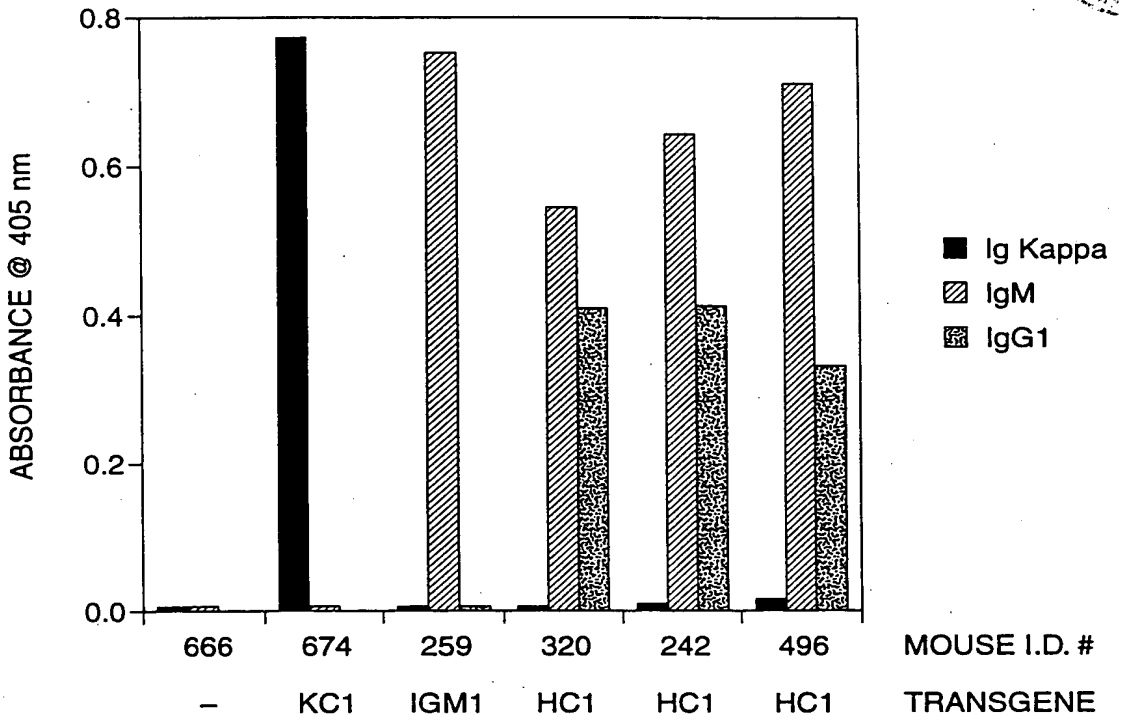

ABSORBANCE @ 405 nm
0.8
0.6
0.4
0.2
0.0
Ig Kappa
IgM
IgG1
666 674 259 320 242 496 MOUSE I.D. #
– KC1 IGM1 HC1 HC1 HC1 TRANSGENE

FIG. 34

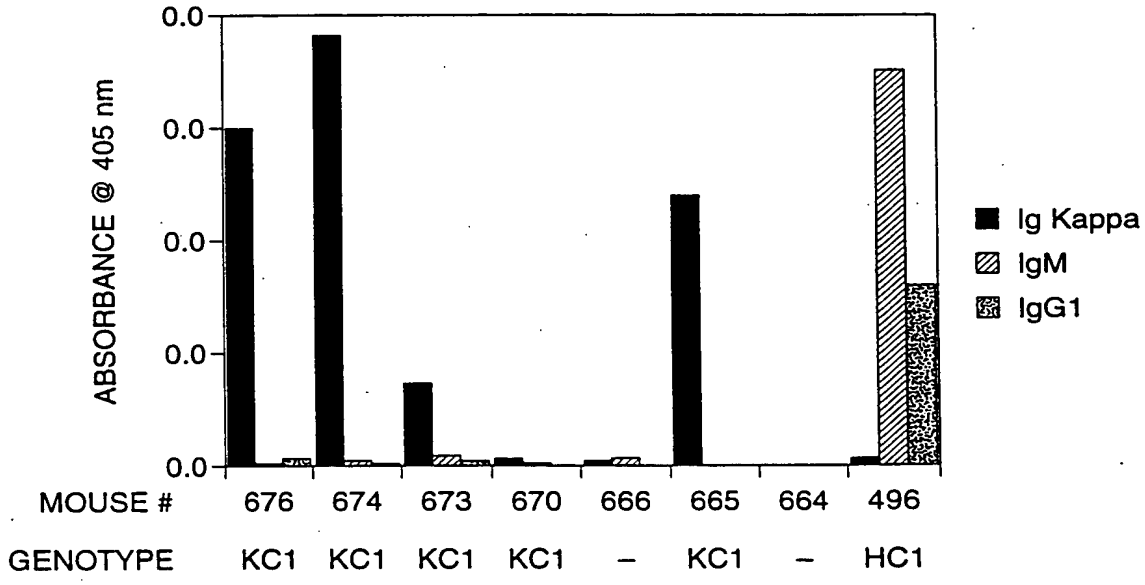

ABSORBANCE @ 405 nm
0.0
0.0
0.0
0.0
0.0
Ig Kappa
IgM
IgG1
MOUSE # 676 674 673 670 666 665 664 496
GENOTYPE KC1 KC1 KC1 KC1 – KC1 – HC1

FIG. 35

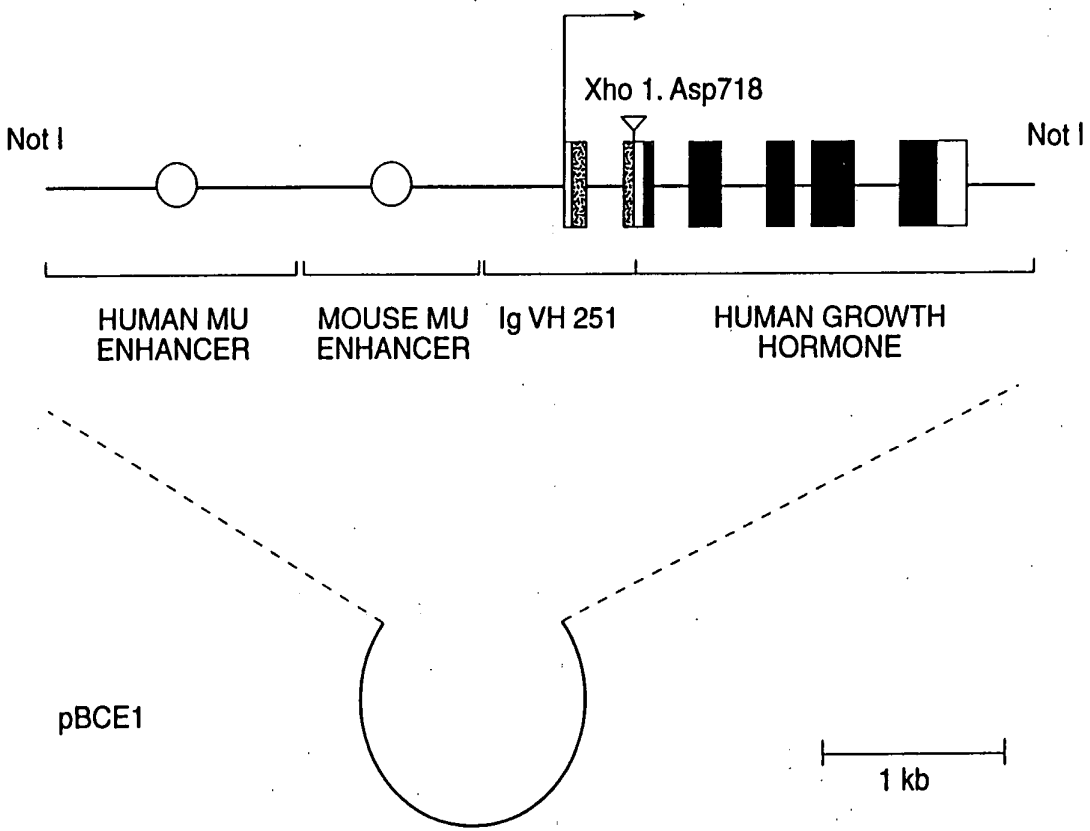

Xho 1. Asp718
Not I
Not I
HUMAN MU ENHANCER
MOUSE MU ENHANCER
Ig VH 251
HUMAN GROWTH HORMONE
pBCE1
1 kb

FIG. 36

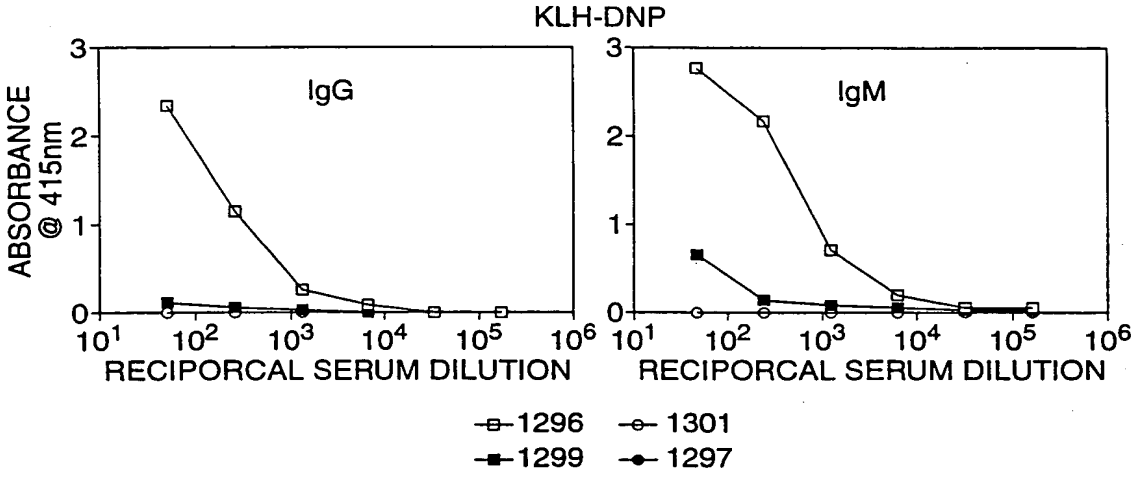


FIG. 37A

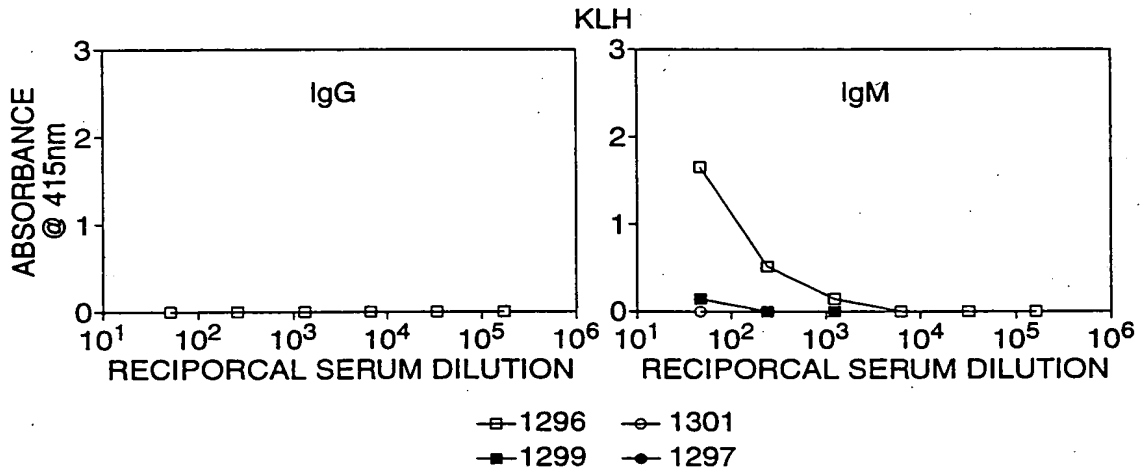


FIG. 37B

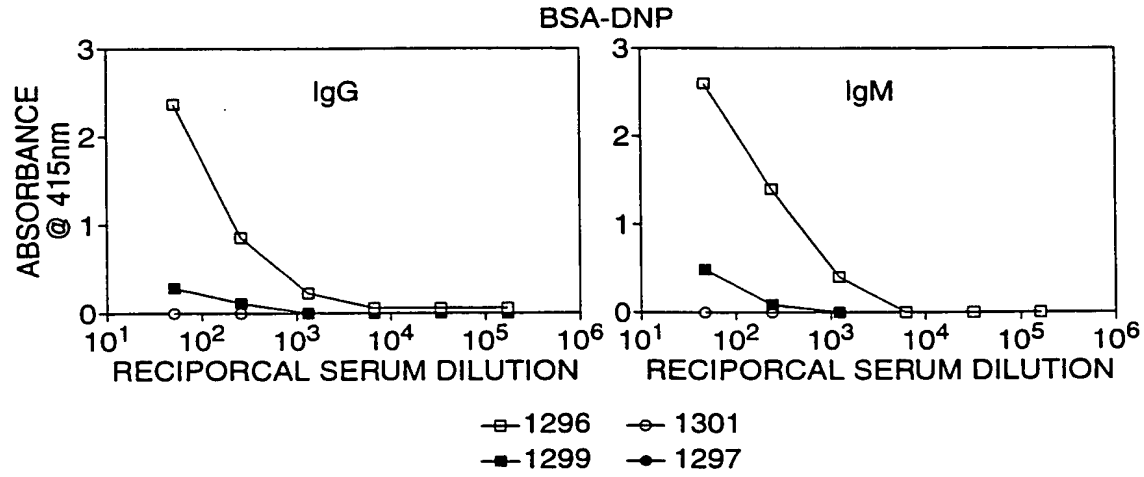


FIG. 37C

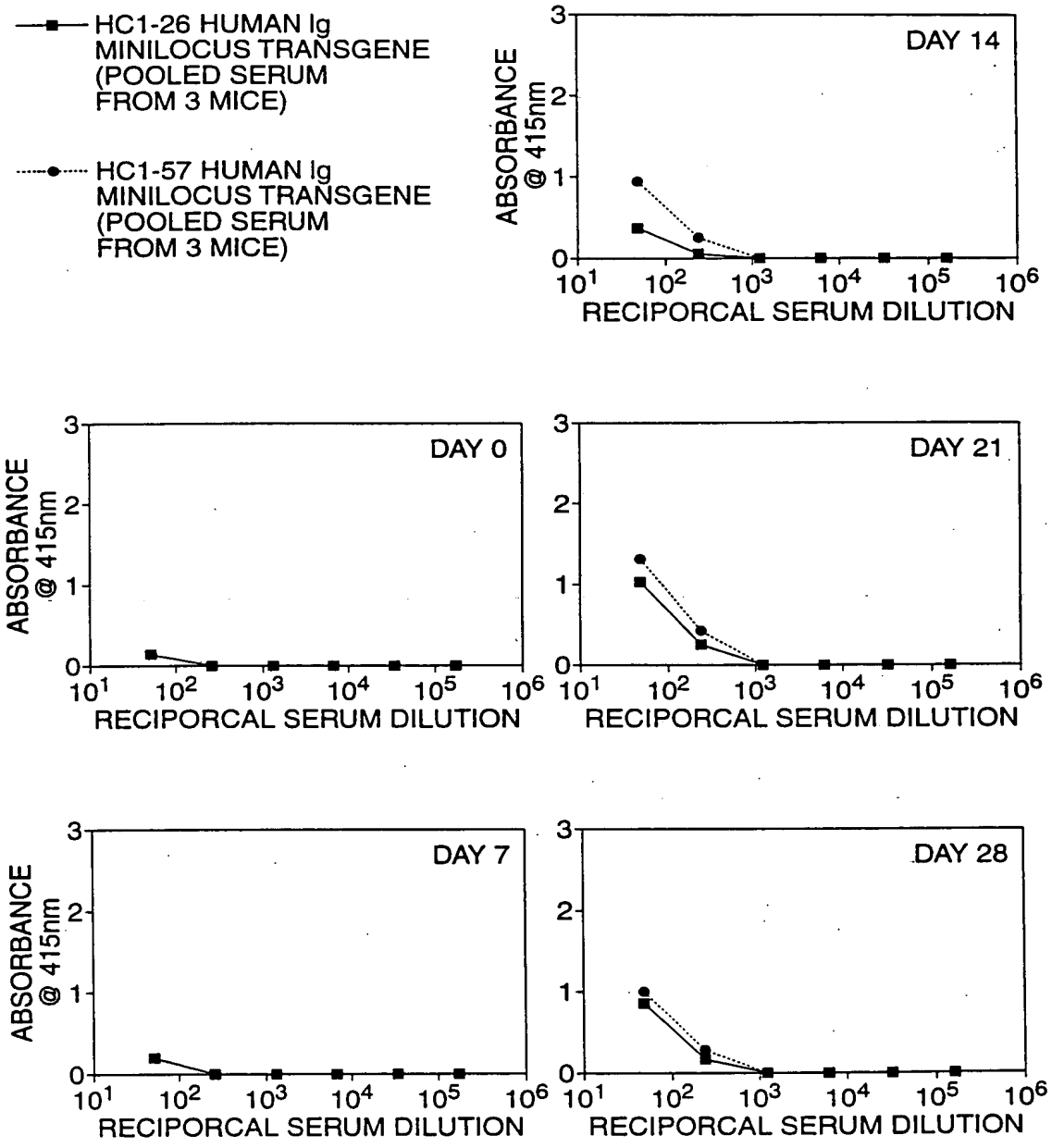

HC1-26 HUMAN Ig MINILOCUS TRANSGENE (POOLED SERUM FROM 3 MICE)
HC1-57 HUMAN Ig MINILOCUS TRANSGENE (POOLED SERUM FROM 3 MICE)
DAY 14
DAY 0
DAY 21
DAY 7
DAY 28
ABSORBANCE @ 415nm
RECIPORCAL SERUM DILUTION
0
1
2
3
10^1
10^2
10^3
10^4
10^5
10^6

FIG. 38

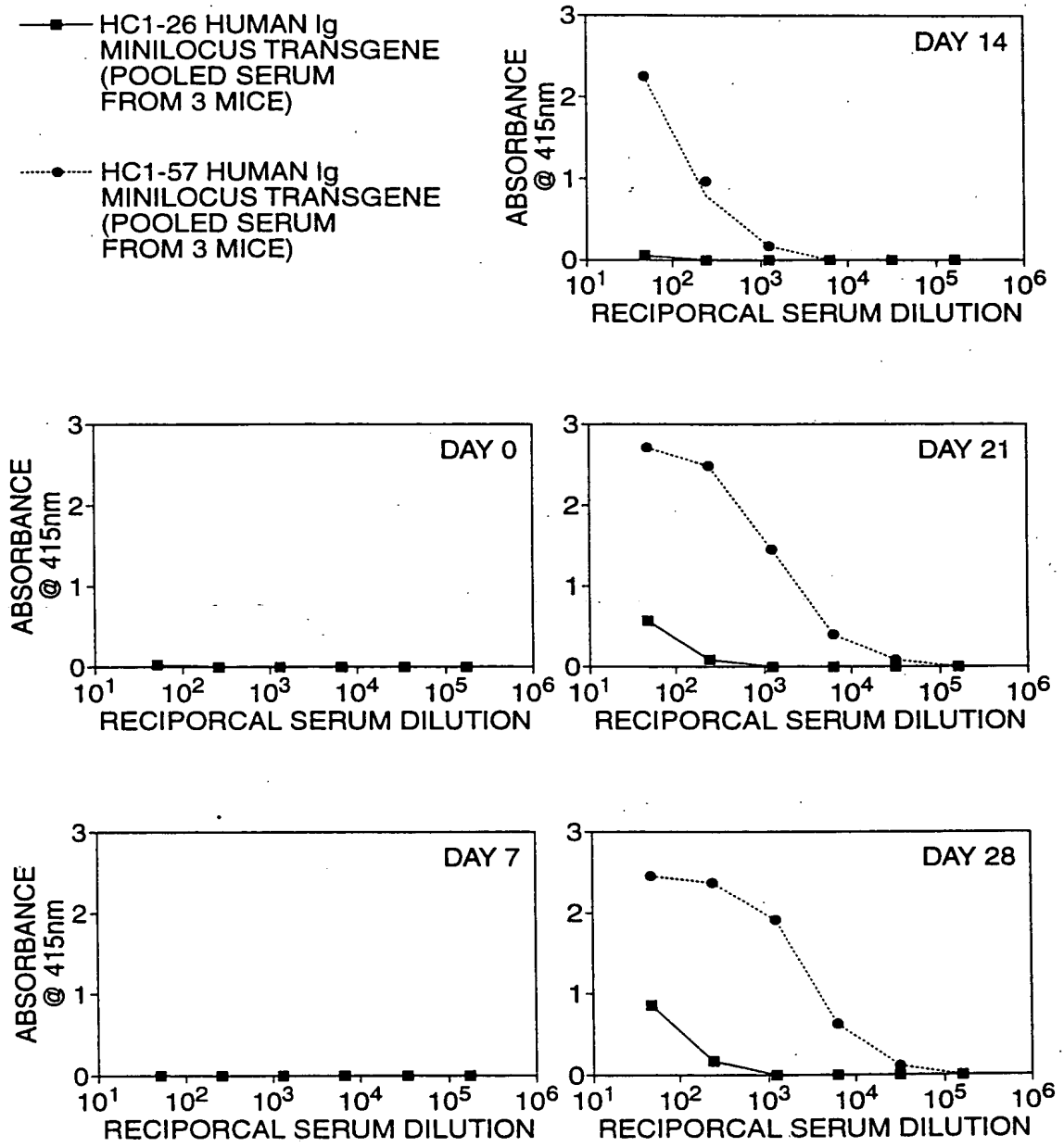

HC1-26 HUMAN Ig MINILOCUS TRANSGENE (POOLED SERUM FROM 3 MICE)
HC1-57 HUMAN Ig MINILOCUS TRANSGENE (POOLED SERUM FROM 3 MICE)
DAY 14
DAY 0
DAY 21
DAY 7
DAY 28
ABSORBANCE @ 415nm
RECIPORCAL SERUM DILUTION
0
1
2
3
10^1
10^2
10^3
10^4
10^5
10^6

FIG. 39

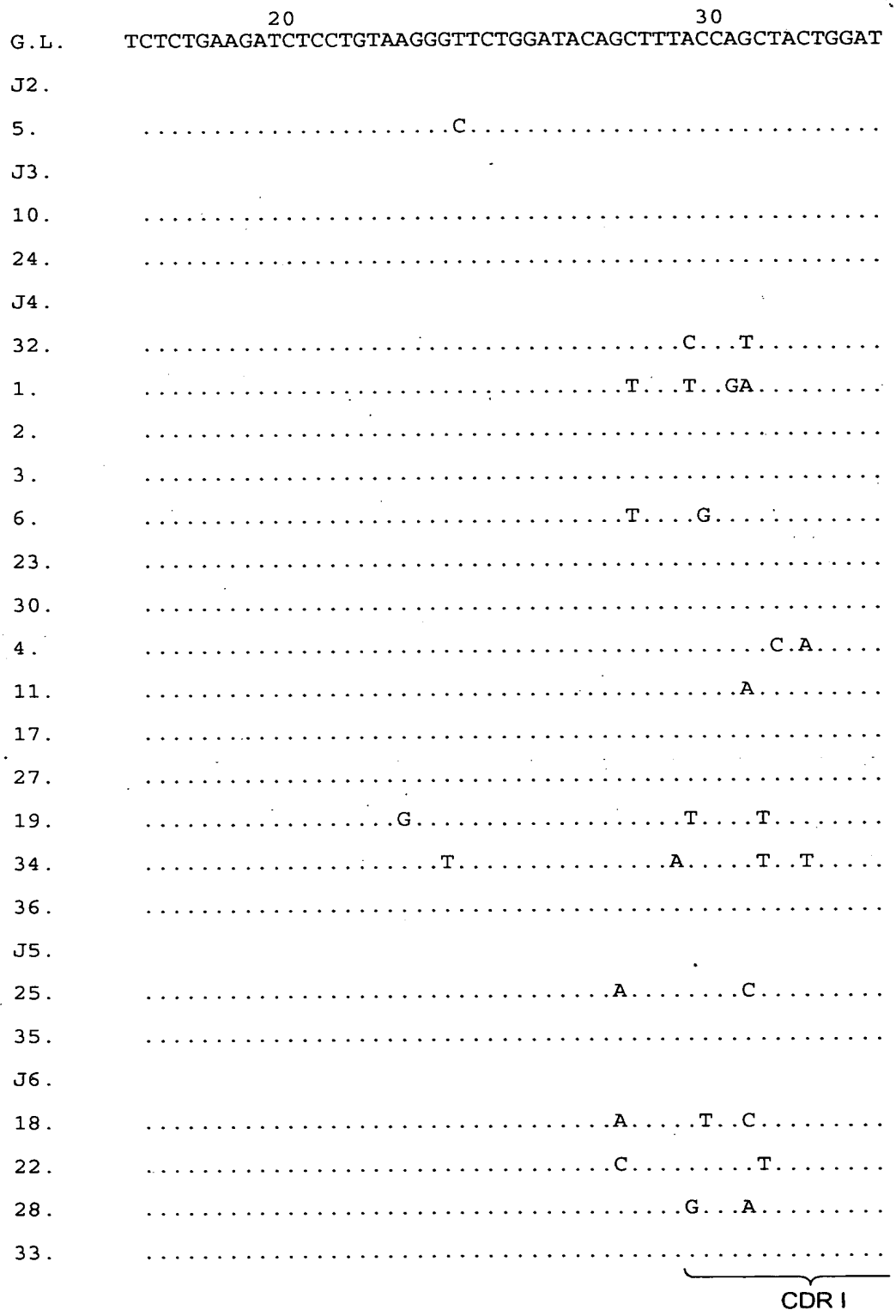

20
30
G.L. TCTCTGAAGATCTCCTGTAAGGGTTCTGGATACAGCTTTACCAGCTACTGGAT
J2.
5. .....C.....
J3.
10. .....
24. .....
J4.
32. .....C...T.....
1. .....T...T..GA.....
2. .....
3. .....
6. .....T....G.....
23. .....
30. .....
4. .....C.A.....
11. .....A.....
17. .....
27. .....
19. .....G.....T....T.....
34. .....T.....A.....T..T.....
36. .....
J5.
25. .....A.....C.....
35. .....
J6.
18. .....A.....T..C.....
22. .....C.....T.....
28. .....G...A.....
33. .....
CDR I

FIG. 40A

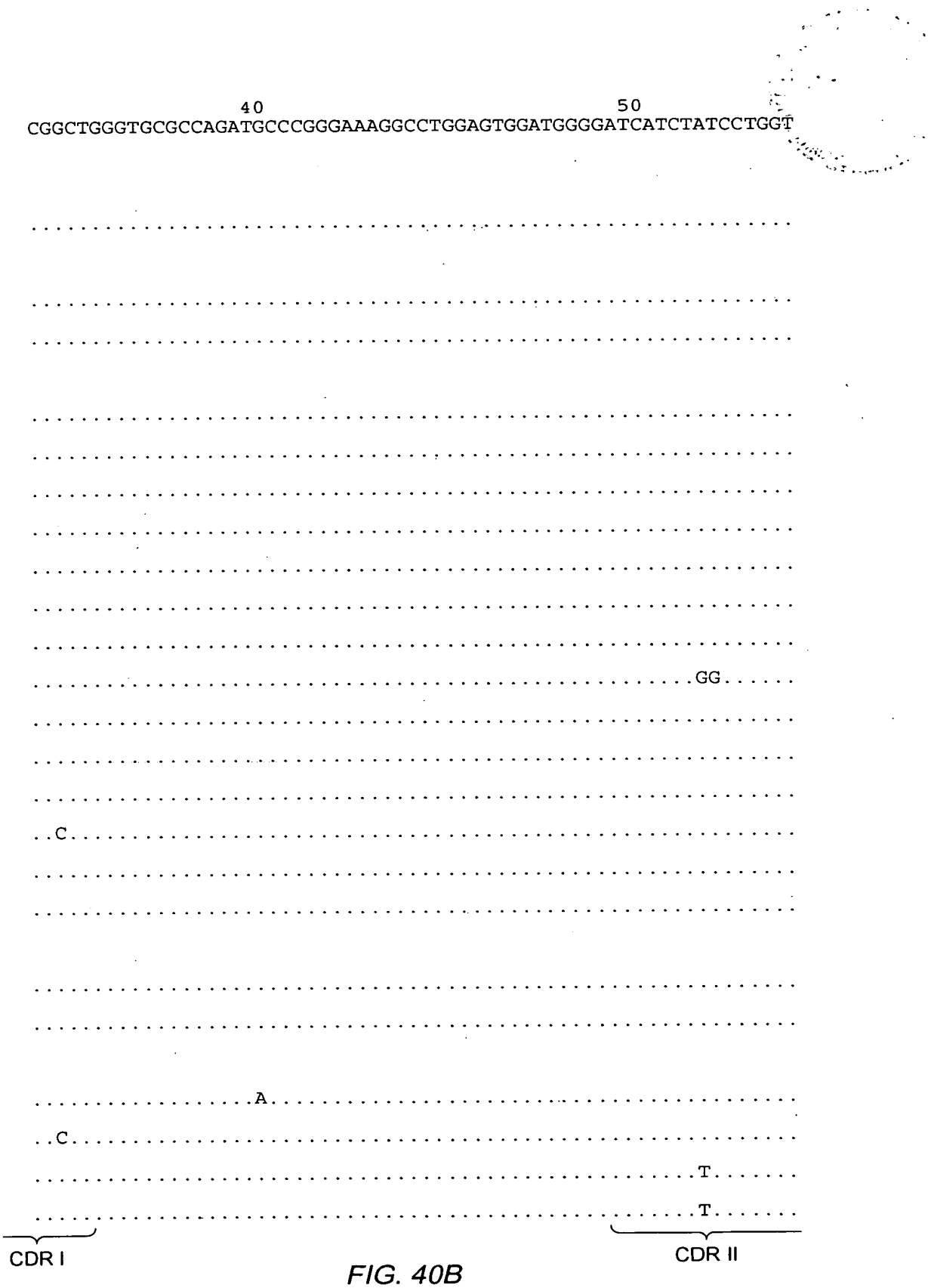

40
50
CGGCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGGGGATCATCTATCCTGGT
GG
C
A
C
T
T
CDR I
CDR II

FIG. 40B

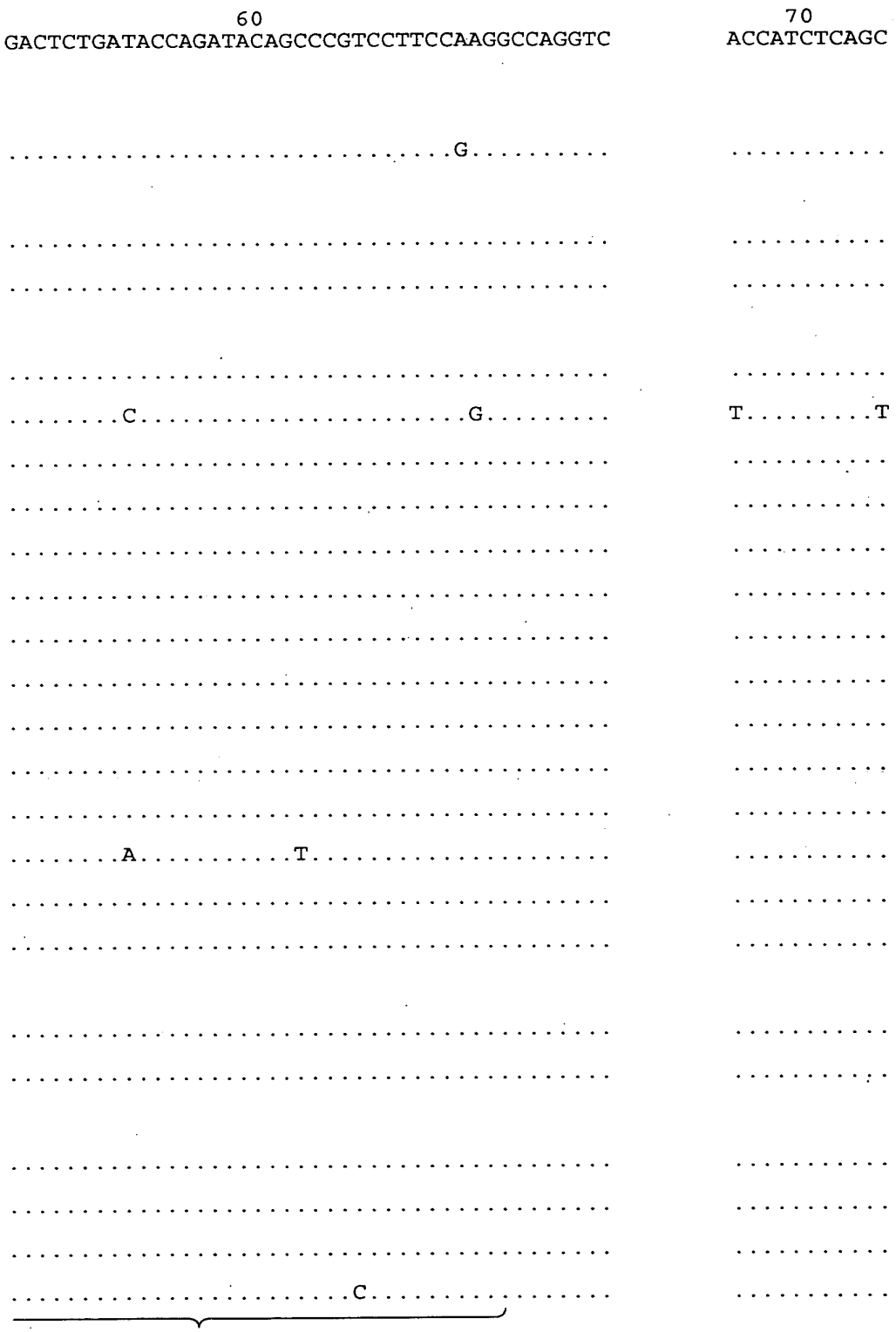

60
GACTCTGATACCAGATACAGCCCGTCCTTCCAAGGCCAGGTC
70
ACCATCTCAGC
G
C
G
T
T
A
T
C
CDR II

FIG. 40C

```
                        80                            90
CGACAAGTCCATCAGCACCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCTCGGACACCGCC

...........................CG................................

.............................................................
............................................G...........GT.T.

.............................................................
..............A........T...........A..C....G....T............
.............................................................
.............................................................
.............................................................
...............T............................G................
.............................................................
...............T.............................................
...............G.............................................
.............................................................
.............................................................
.............................................................
.............................................................
.............................................................

..........G..................................................
.............................................................

.............................................................
.............................................................
......C......................................................
..............A..............................................
```

FIG. 40D

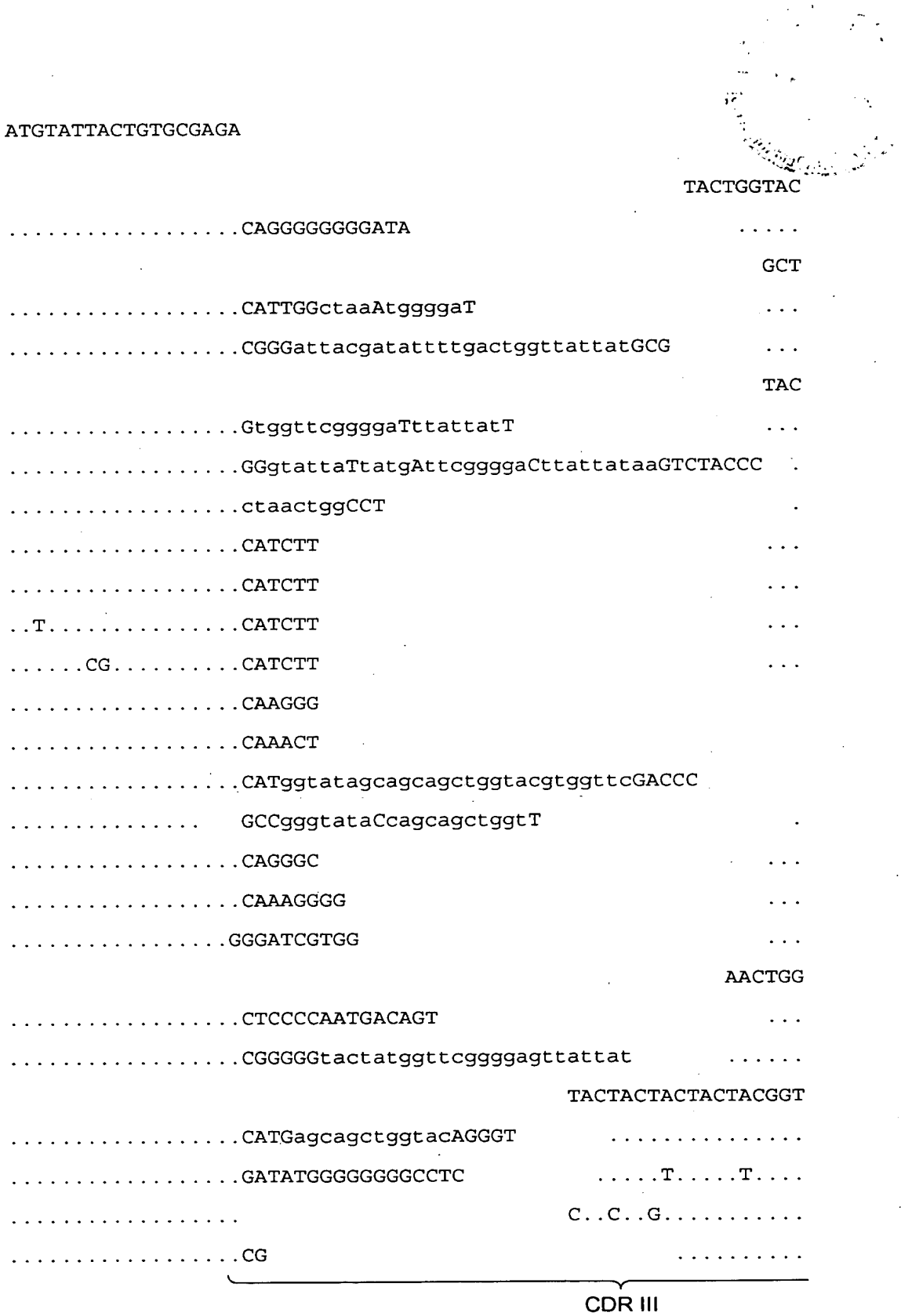

ATGTATTACTGTGCGAGA
TACTGGTAC
.....CAGGGGGGGGATA.....
GCT
.....CATTGGctaaAtggggaT...
.....CGGGattacgatattttgactggttattatGCG...
TAC
.....GtggttcggggaTttattatT...
.....GGgtattaTtatgAttcggggaCttattataaGTCTACCC.
.....ctaactggCCT.
.....CATCTT...
.....CATCTT...
..T.....CATCTT...
.....CG.....CATCTT...
.....CAAGGG
.....CAAACT
.....CATggtatagcagcagctggtacgtggttcGACCC
..... GCCgggtataCcagcagctggtT.
.....CAGGGC...
.....CAAAGGGG...
.....GGGATCGTGG...
AACTGG
.....CTCCCCAATGACAGT...
.....CGGGGGtactatggttcggggagttattat.....
TACTACTACTACTACGGT
.....CATGagcagctggtacAGGGT.....
.....GATATGGGGGGGGCCTC.....T.....T....
.....C..C..G.....
.....CG.....
CDR III

FIG. 40E

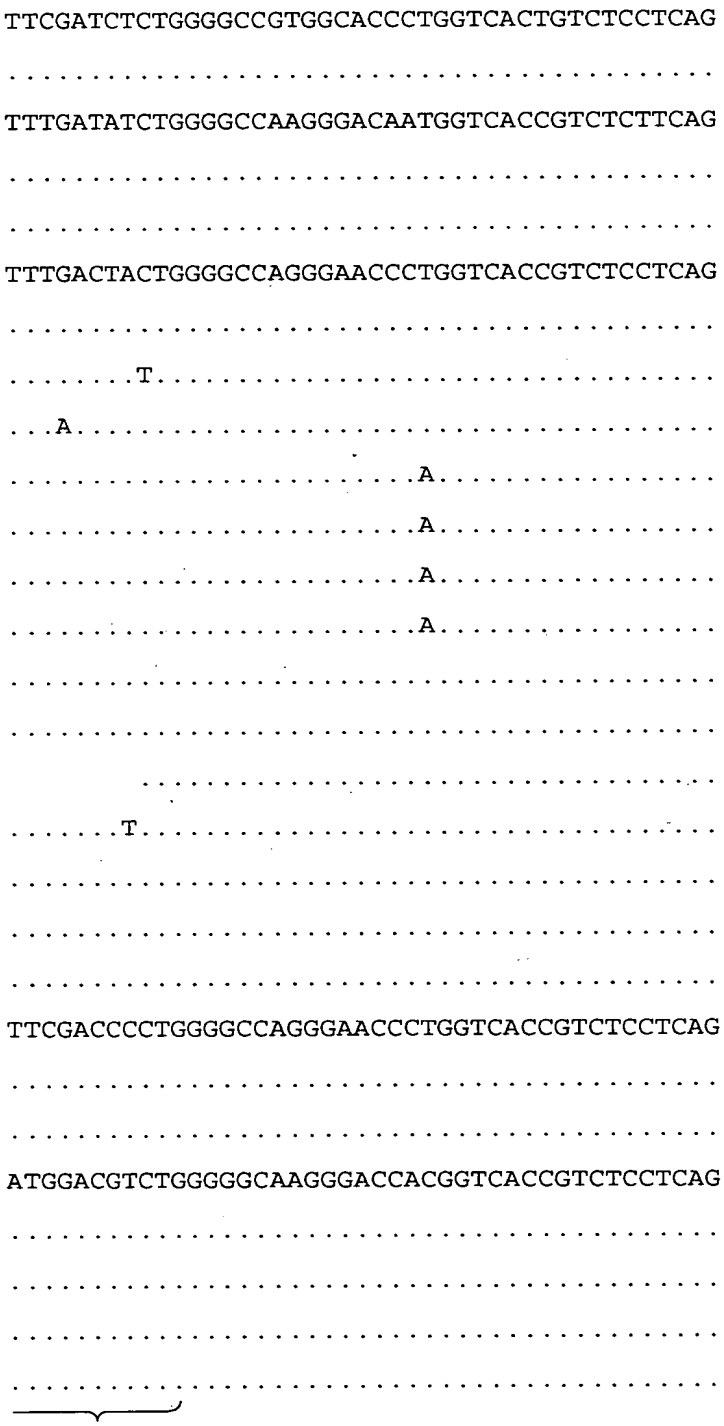
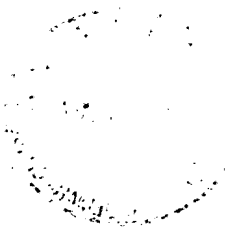

TTCGATCTCTGGGGCCGTGGCACCCTGGTCACTGTCTCCTCAG
TTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCAG
TTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAG
TTCGACCCCTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAG
ATGGACGTCTGGGGGCAAGGGACCACGGTCACCGTCTCCTCAG
CDR III

FIG. 40F



```
TTTTCTGGCC TGACAACCAG GGTGGCGCAG GATGCTCAGT GCAGAGAGGA    50

AGAAGCAGGT GGTCTCTGCA GCTGGAAGCT CAGCTCCCAC CCAGCTGCTT   100

TGCATGTCCC TCCCAGCTGC CCTACCTTCC AGAGCCCATA TCAATGCCTG   150

TGTCAGAGCC CTGGGGAGGA ACTGCTCAGT TAGGACCCAG AGGGAACCAT   200
                                                    Me
GGAAGCCCCA GCTCAGCTTC TCTTCCTCCT GCTACTCTGG CTCCCAGgtg   250
tGluAlaPro AlaGlnLeuL euPheLeuLe uLeuLeuTrp LeuPro
aggggggaacc atgaggtggt tttgcacatt agtgaaaact cttgccacct   300

ctgctcagca agaaatataa ttaaaattca aagtatatca acaattttgg   350

ctctactcaa agacagttgg tttgatcttg attacatgag tgcatttctg   400

ttttatttcc aatttcagAT ACCACCGGAG AAATTGTGTT GACACAGTCT   450
                 Asp ThrThrGlyG luIleValLe uThrGlnSer
CCAGCCACCC TGTCTTTGTC TCCAGGGGAA AGAGCCACCC TCTCCTGCAG   500
ProAlaThrL euSerLeuSe rProGlyGlu ArgAlaThrL euSerCysAr
GGCCAGTCAG AGTGTTAGCA GCTACTTAGC CTGGTACCAA CAGAAACCTG   550
gAlaSerGln SerValSerS erTyrLeuAl aTrpTyrGln GlnLysProG
GCCAGGCTCC CAGGCTCCTC ATCTATGATG CATCCAACAG GGCCACTGGC   600
lyGlnAlaPr oArgLeuLeu IleTyrAspA laSerAsnAr gAlaThrGly
ATCCCAGCCA GGTTCAGTGG CAGTGGGTCT GGGACAGACT TCACTCTCAC   650
IleProAlaA rgPheSerGl ySerGlySer GlyThrAspP heThrLeuTh
CATCAGCAGC CTAGAGCCTG AAGATTTTGC AGTTTATTAC TGTCAGCAGC   700
rIleSerSer LeuGluProG luAspPheAl aValTyrTyr CysGlnGlnA
GTAGCAACTG GCCTCCCACA GTGATTCCAC ATGAAACAAA AACCCCAACA   750
rgSerAsnTr pPro
AGACCATCAG TGTTTACTAG ATTATTATAC CAGCTGCTTC CTTTACAGAC   800

AGCTAGTGGG GT                                           812
```

FIG. 41

```
AGGGCGGCGC AGATGCTCAG TGCAGAGAGA AGAAACAGGT GGTCTCTGCA   50

GCTGGAAGCT CAGCTCCCAC CCCAGCTGCT TTGCATGTCC CTCCCAGCTG  100

CCCTACCTTC CAGAGCCCAT ATCAATGCCT GGGTCAGAGC TCTGGGGAGG  150

AACTGCTCAG TTAGGACCCA GACGGAACCA TGGAAGCCCC AGCGCAGCTT  200
                                  M etGluAlaPr oAlaGlnLeu
CTCTTCCTCC TGCTACTCTG GCTCACAGgt gaggggaata tgaggtgtct  250
LeuPheLeuL euLeuLeuTr pLeuThr
ttgcacatca gtgaaaactc ctgccacctc tgctcagcaa gaaatataat  300

taaaattcaa aatagatcaa caattttggc tctactcaaa gacagtgggt  350

ttgattttga ttacatgagt gcatttctgt tttatttcca atttcagATA  400
                                                    AspT
CCACCGGAGA AATTGTGTTG ACACAGTCTC CAGCCACCCT GTCTTTGTCT  450
hrThrGlyGl uIleValLeu ThrGlnSerP roAlaThrLe uSerLeuSer
CCAGGGGAAA GAGCCACCCT CTCCTGCAGG GCCAGTCAGG GTGTTAGCAG  500
ProGlyGluA rgAlaThrLe uSerCysArg AlaSerGlnG lyValSerSe
CTACTTAGCC TGGTACCAGC AGAAACCTGG CCAGGCTCCC AGGCTCCTCA  550
rTyrLeuAla TrpTyrGlnG lnLysProGl yGlnAlaPro ArgLeuLeuI
TCTATGATGC ATCCAACAGG GCCACTGGCA TCCCAGCCAG GTTCAGTGGC  600
leTyrAspAl aSerAsnArg AlaThrGlyI lePro AlaAr gPheSerGly
AGTGGGCCTG GGACAGACTT CACTCTCACC ATCAGCAGCC TAGAGCCTGA  650
SerGlyProG lyThrAspPh eThrLeuThr IleSerSerL euGluProGl
AGATTTTGCA GTTTATTACT GTCAGCAGCG TAGCAACTGG CATCCCACAG  700
uAspPheAla ValTyrTyrC ysGlnGlnAr gSerAsnTrp His
TGATTCCACA TGAAACAAAA ACCCCAACAA GACCATCAGT GTTTACTAGA  750

TTATTATACC AGCTGCTTCC TTTACAGACA GCTAGTGGGG TGGCCACTCA  800

GTGTTAGCAT CTCAGCTCTA TTTGGCCATT TTGGAGTTCA AGTTGTCAAG  850

TCCAAAATTA CTTATGTTAG TCCATTGCAT CATACCATTT CAGTGTGGCT  900
```

FIG. 42

```
CCGCCCCAGC TGCTTTGCAT GTCCCTCCCA GCCGCCCTGC AGTCCAGAGC    50

CCATATCAAT GCCTGGGTCA GAGCTCTGGA GAAGAGCTGC TCAGTTAGGA   100

ACCCCAGAGG GAACCATGGA AACCCCAGCG CAGCTTCTCT TCCTCCTGCT   150
                MetGl uThrProAla GlnLeuLeuP heLeuLeuLe
ACTCTGGCTC CCAGgtgagg ggaacatggg atggttttgc atgtcagtga   200
uLeuTrpLeu Pro
aaaccctctc aagtcctgtt acctggcaac tctgctcagt caatacaata   250

attaaagctc aatataaagc aataattctg gctcttctgg gaagacaatg   300

ggtttgattt agattacatg ggtgactttt ctgttttatt tccaatctca   350

gATACCACCG GAGAAATTGT GTTGACGCAG TCTCCAGGCA CCCTGTCTTT   400
AspThrThrG lyGluIleVa lLeuThrGln SerProGlyT hrLeuSerLe
GTCTCCAGGG GAAAGAGCCA CCCTCTCCTG CAGGGCCAGT CAGAGTGTTA   450
uSerProGly GluArgAlaT hrLeuSerCy sArgAlaSer GlnSerValS
GCAGCAGCTA CTTAGCCTGG TACCAGCAGA AACCTGGCCA GGCTCCCAGG   500
erSerSerTy rLeuAlaTrp TyrGlnGlnL ysProGlyGl nAlaProArg
CTCCTCATCT ATGGTGCATC CAGCAGGGCC ACTGGCATCC CAGACAGGTT   550
LeuLeuIleT yrGlyAlaSe rSerArgAla ThrGlyIleP roAspArgPh
CAGTGGCAGT GGGTCTGGGA CAGACTTCAC TCTCACCATC AGCAGACTGG   600
eSerGlySer GlySerGlyT hrAspPheTh rLeuThrIle SerArgLeuG
AGCCTGAAGA TTTTGCAGTG TATTACTGTC AGCAGTATGG TAGCTCACCT   650
luProGluAs pPheAlaVal TyrTyrCysG lnGlnTyrGl ySerSerPro
CCCACAGTGA TTCAGCTTGA AACAAAAACC TCTGCAAGAC CTTCATTGTT   700

TACTAGATTA TACCAGCTGC TTCCTTTACA GATAGCTGCT GCAATGACAA   750

CTCAATTTAG CATCTCTCTC TGCTTGGGCA TTTTGGGGAT CTTAAAAAAG   800

TAATCCCTTG ATATATTTTT GACTCTGATT CCTGCATTTT TCCTCAGACC   850

AAGATGGACA GCCAGGTTTA AGCACAGTTT CACAGTAATG GCCACTGGAT   900
```

FIG. 43

```
AAACACATTC TCTGCAGACA AATTTGAGCT ACCTTGATCT TACCTGGACA    50

GGTGGGGACA CTGAGCTGGT GCTGAGTTAC TCAGATGCGC CAGCTCTGCA   100

GCTGTGCCCA GCCTGCCCCA TCCCCTGCTC ATTTGCATGT TCCCAGAGCA   150

CAACCTCCTG CCCTGAAGCC TTATTAATAG GCTGGTCAGA CTTTGTGCAG   200

GAATCAGACC CAGTCAGGAC ACAGCATGGA CATGAGGGTC CTCGCTCAGC   250
                            MetAs pMetArgVal LeuAlaGlnL
TCCTGGGGCT CCTGCTGCTC TGTTTCCCAG gtaaggatgg agaacactag   300
euLeuGlyLe uLeuLeuLeu CysPhePro
cagtttactc agcccagggt gctcagtact gctttactat tcagggaaat   350

tctcttacaa catgattaat tgtgtggaca tttgttttta tgtttccaat   400

ctcagGTGCC AGATGTGACA TCCAGATGAC CCAGTCTCCA TCCTCACTGT   450
    GlyAla ArgCysAspI leGlnMetTh rGlnSerPro SerSerLeuS
CTGCATCTGT AGGAGACAGA GTCACCATCA CTTGTCGGGC GAGTCAGGGT   500
erAlaSerVa lGlyAspArg ValThrIleT hrCysArgAl aSerGlnGly
ATTAGCAGCT GGTTAGCCTG GTATCAGCAG AAACCAGAGA AAGCCCCTAA   550
IleSerSerT rpLeuAlaTr pTyrGlnGln LysProGluL ysAlaProLy
GTCCCTGATC TATGCTGCAT CCAGTTTGCA AAGTGGGGTC CCATCAAGGT   600
sSerLeuIle TyrAlaAlaS erSerLeuGl nSerGlyVal ProSerArgP
TCAGCGGCAG TGGATCTGGG ACAGATTTCA CTCTCACCAT CAGCAGCCTG   650
heSerGlySe rGlySerGly ThrAspPheT hrLeuThrIl eSerSerLeu
CAGCCTGAAG ATTTTGCAAC TTATTACTGC CAACAGTATA ATAGTTACCC   700
GlnProGluA spPheAlaTh rTyrTyrCys GlnGlnTyrA snSerTyrPr
ACCCACAGTG TTACACACCC AAACATAAAC CCCCAGGGAA GCAGATGTGT   750
o
GAGGCTGGGC TGCCCCAGCT GCTTCTCCTG ATGCCTCCAT CAGCTGAGAG   800

TGTTCCTCAG ATGCAGCCAC ACTCTGATGG TGTTGGTAGA TGGGGAC      847
```

FIG. 44

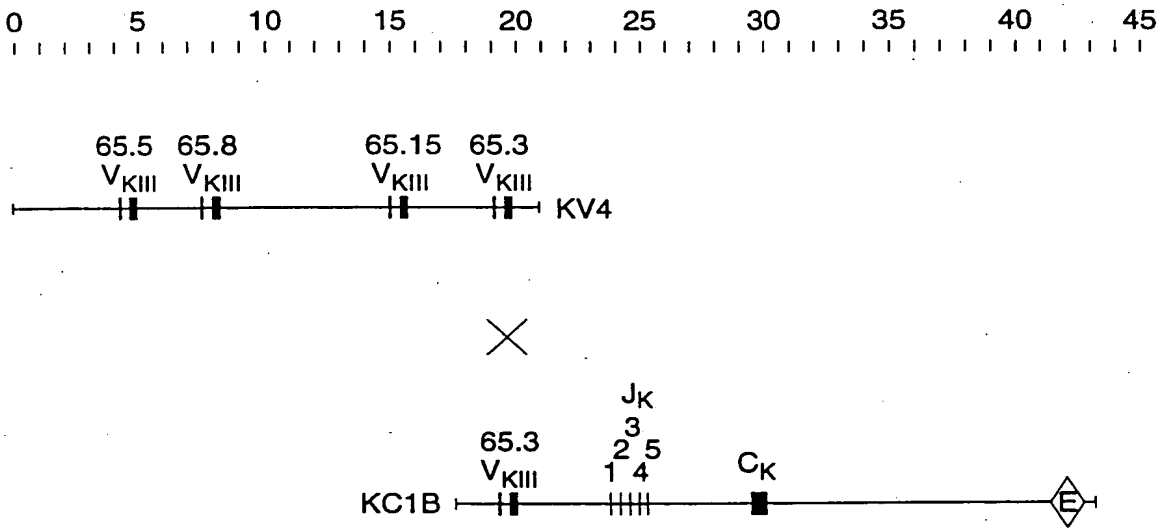

0
5
10
15
20
25
30
35
40
45
65.5 V_{KIII}
65.8 V_{KIII}
65.15 V_{KIII}
65.3 V_{KIII}
KV4
J_K
3
2
5
1
4
65.3 V_{KIII}
C_K
KC1B
E

FIG. 45

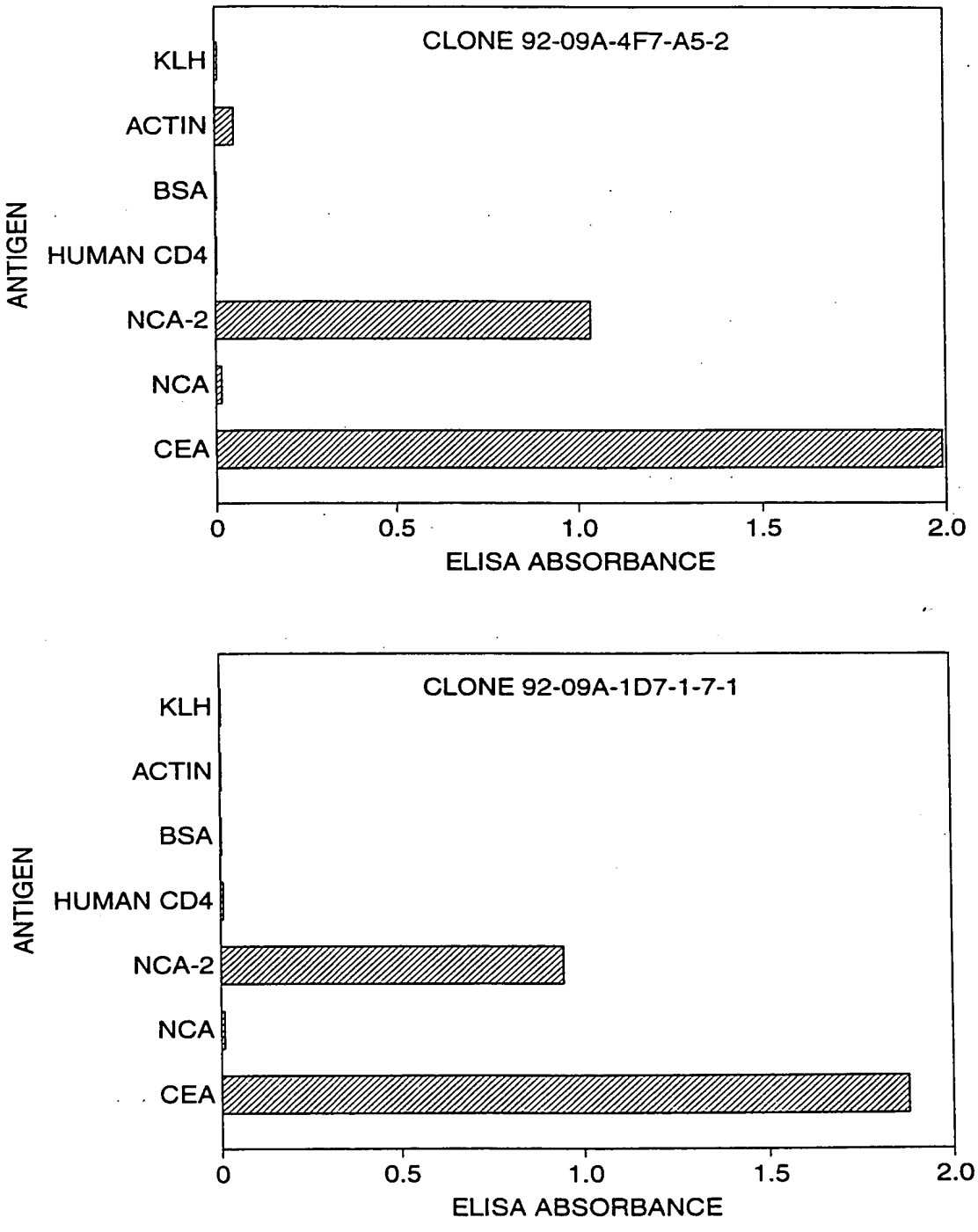

CLONE 92-09A-4F7-A5-2
KLH
ACTIN
BSA
HUMAN CD4
NCA-2
NCA
CEA
ANTIGEN
0
0.5
1.0
1.5
2.0
ELISA ABSORBANCE
CLONE 92-09A-1D7-1-7-1
KLH
ACTIN
BSA
HUMAN CD4
NCA-2
NCA
CEA
ANTIGEN
0
0.5
1.0
1.5
2.0
ELISA ABSORBANCE

FIG. 46

					HUMAN			MOUSE
				VH251	n D n		J	Cγ
5	DXP'1	J6	G1	GCCTCGGACACCGCCATGTATTACTGTGtGAGA	cattTATGGTTCGGGGAGTTAcg		CGGTgTGaACGTCTGGGGGCCAAGGGACCACGGTCACCGTCTCCTCAG	CCAAAACGACACCCCCATCTGTCTATCCACT
7	DHQ52	J3	G1	GCCTCGGACACCGCCATGTATTACTGTGCGAGA	cACTGGGcattggat		GCTcTTGATgTCTGGGGCCAAGGGACAATGcTCACCGTCTCTTCAG	CCAAAACGACACCCCCATCTGTCTATCCACT
2	DHQ52	J3	G2b	GCCTCGGACACCGCCATGTATTACTGTGCGAGA	ACTGGGGAtgat		GCTTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCAG	CCAAAACAACACCCCCATCAGTCTATCCACT
3	D?	J3	G2b	GaCTCGGACACCGCCATGTATTACTGTGCGAGA	caggggagagat		GCTTTAGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCAG	CCAAAACAACACCCCCATCAGTCTATCCACT
4	DXP'1	J4	G2b	GCCTCGGACACCGCCATGTATTAtTGTGtGAGA	catagggACTATatTTCGGGGAGTTATTttcc		TGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAG	CCAAAACAACACCCCCATCAGTCTATCCACT
10	DHQ52	J3	G2b	GCCTCGGACACCGCCATGTATTACTGTGCGAGA	ACTGGGGAtgat		GCTTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCAG	CCAAAACAACACCCCCATCAGTCTATCCACT
1	D?	J3	G3	GCCTCGGACACCGCCATGTATTACTGTGCGAGA	catgggtctatg		GATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCAG	CTACAACAACAGCCCCATCTGTCTATCCCTT
6	DHQ52	J4	G3	GCCTCGGACACCGCCATGTATTACTGTGCGAGA	gagagcggtcACTGGGGAtcg		TTTGACTAtTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAG	CTACAACAACAGCCCCATCTGTCTATCCCTT
8	DIR2	J3	G3	GCCTCGGACACCGCCATGTATTACTGTGCGAGA	aggGACCCCCctgat		GCTTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCAG	CTACAACAACAGCCCCATCTGTCTATCCCTT
9	DIR2r	J6	G3	GCCTCGGACACCGCCATGTATTACTGTGCGAGA	cgGGGGCCT	TACTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAG		CTACAACAACAGCCCCATCTGTCTATCCCTT

FIG. 47

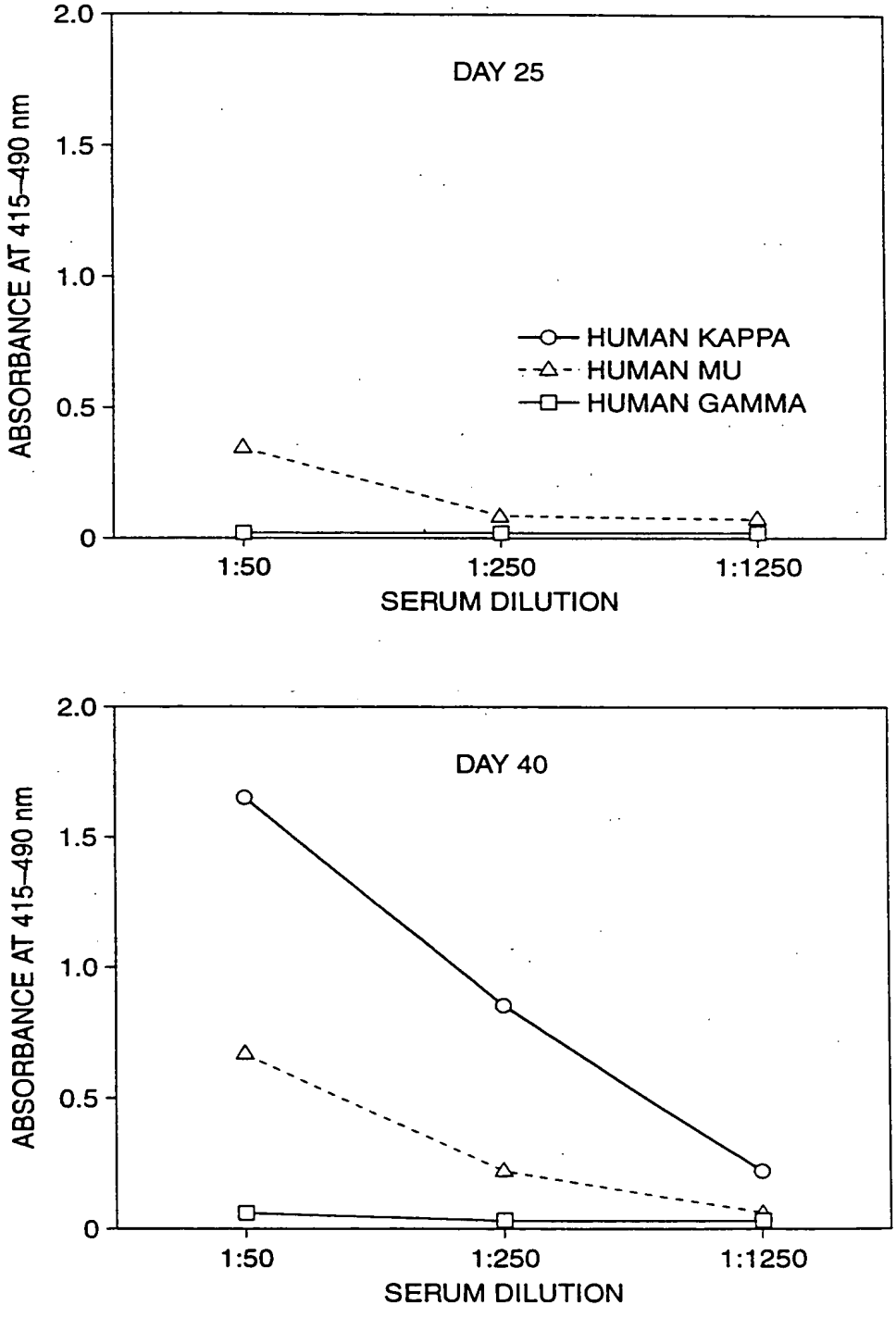

DAY 25
ABSORBANCE AT 415–490 nm
2.0
1.5
1.0
0.5
0
HUMAN KAPPA
HUMAN MU
HUMAN GAMMA
1:50
1:250
1:1250
SERUM DILUTION
DAY 40
ABSORBANCE AT 415–490 nm
2.0
1.5
1.0
0.5
0
1:50
1:250
1:1250
SERUM DILUTION

FIG. 48

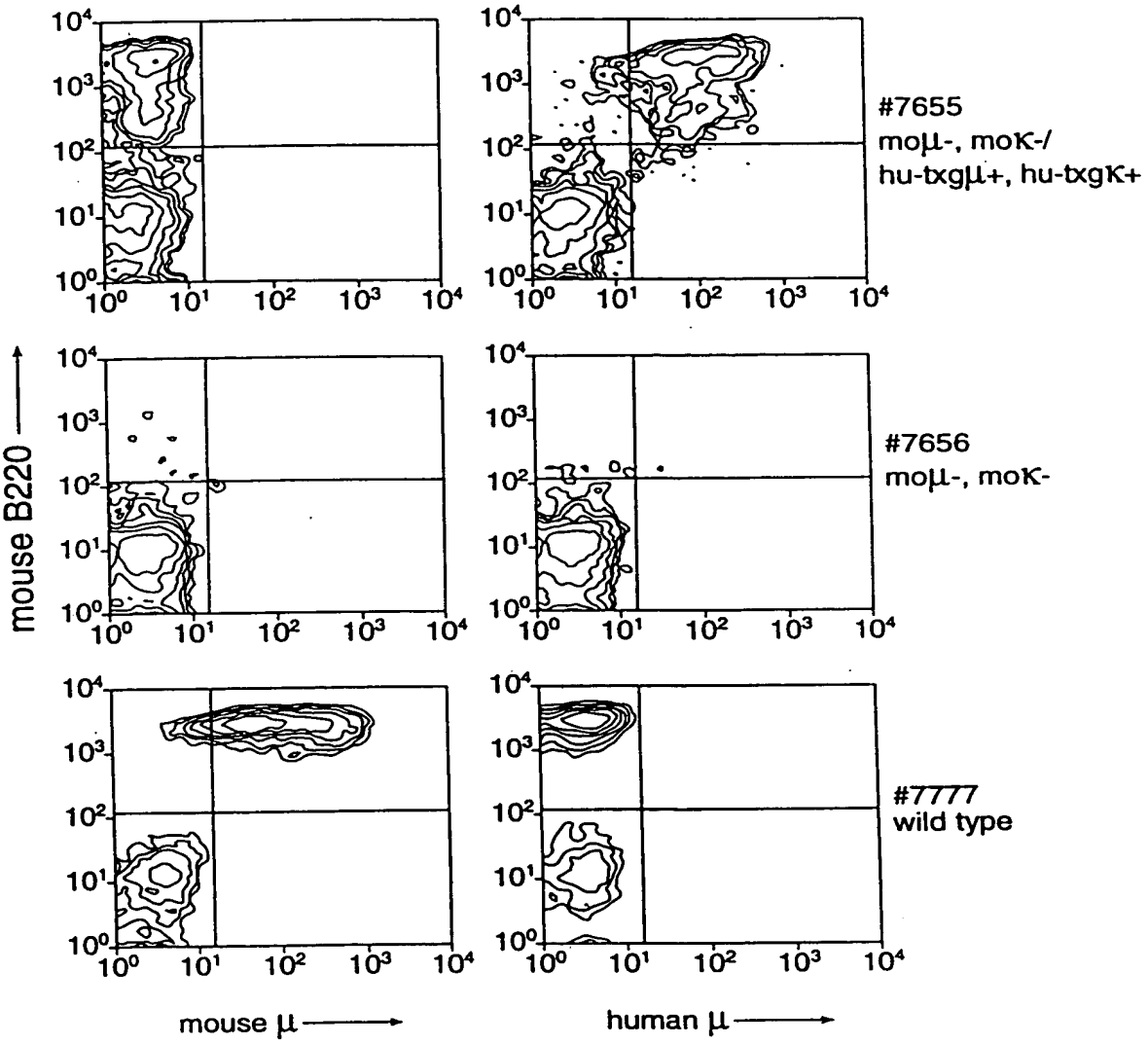


FIG. 49

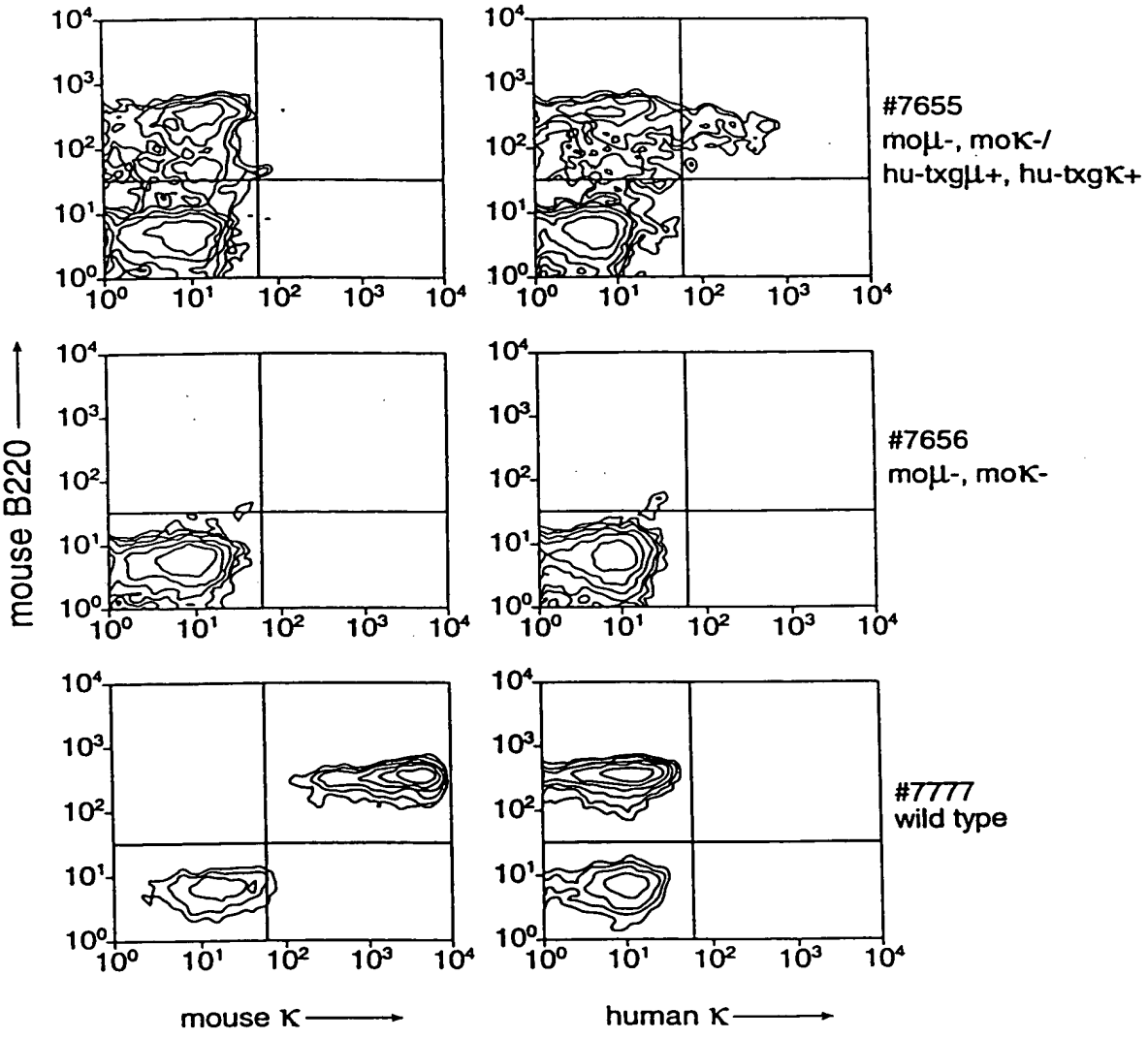


FIG. 50

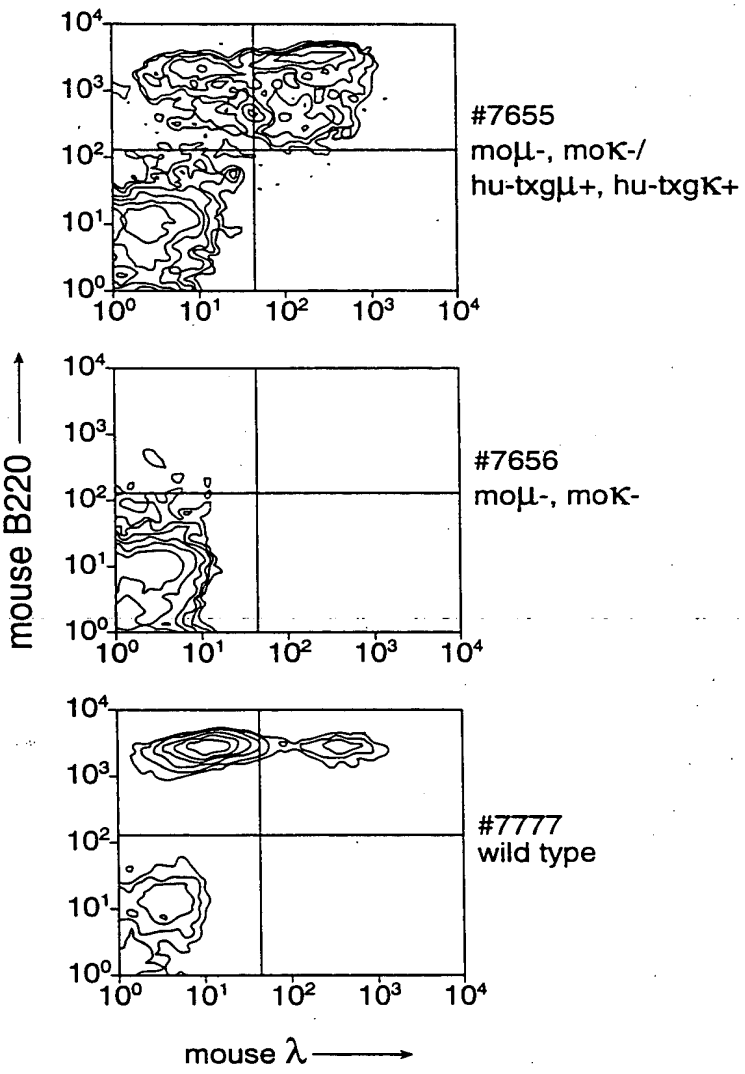

#7655
moμ-, moκ-/
hu-txgμ+, hu-txgκ+
#7656
moμ-, moκ-
#7777
wild type
mouse B220
mouse λ
10^0 10^1 10^2 10^3 10^4

FIG. 51

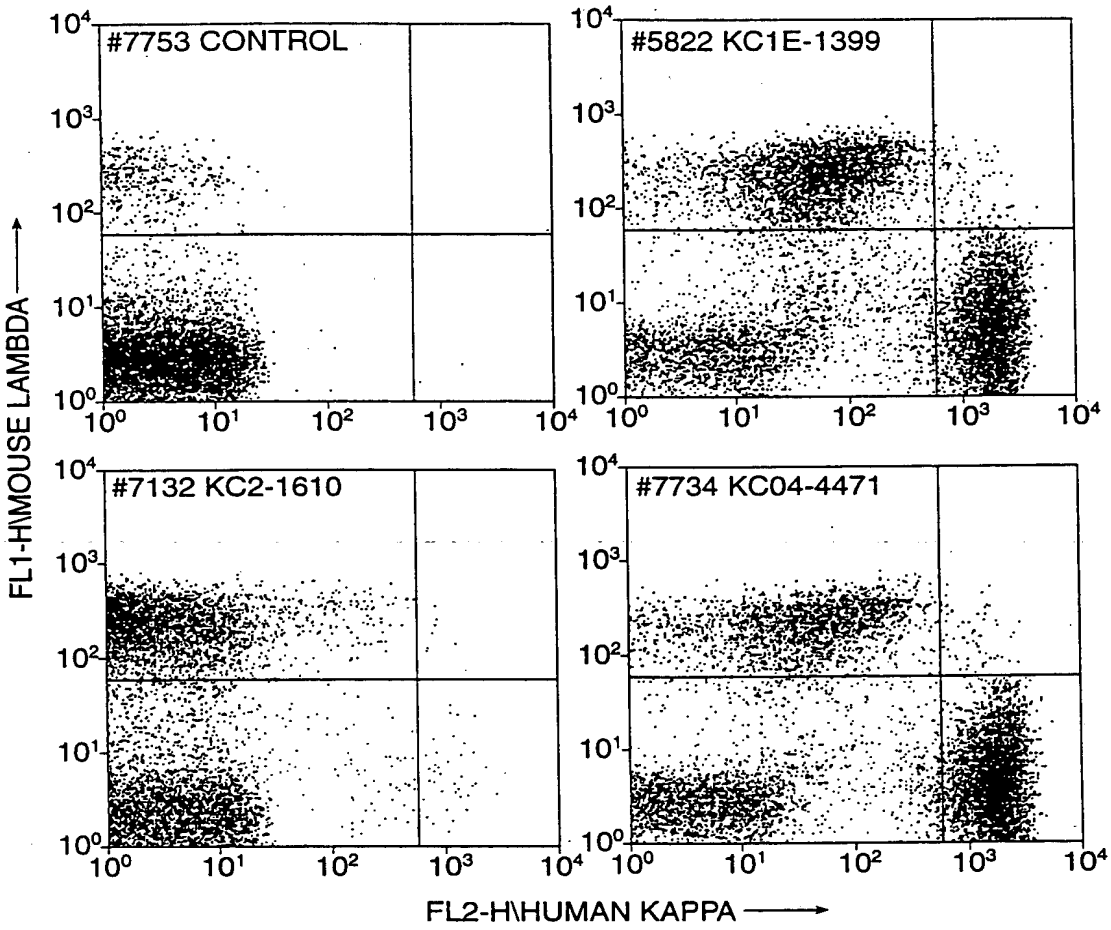

#7753 CONTROL
#5822 KC1E-1399
#7132 KC2-1610
#7734 KC04-4471
FL1-H\MOUSE LAMBDA
FL2-H\HUMAN KAPPA
10^0
10^1
10^2
10^3
10^4

FIG. 52

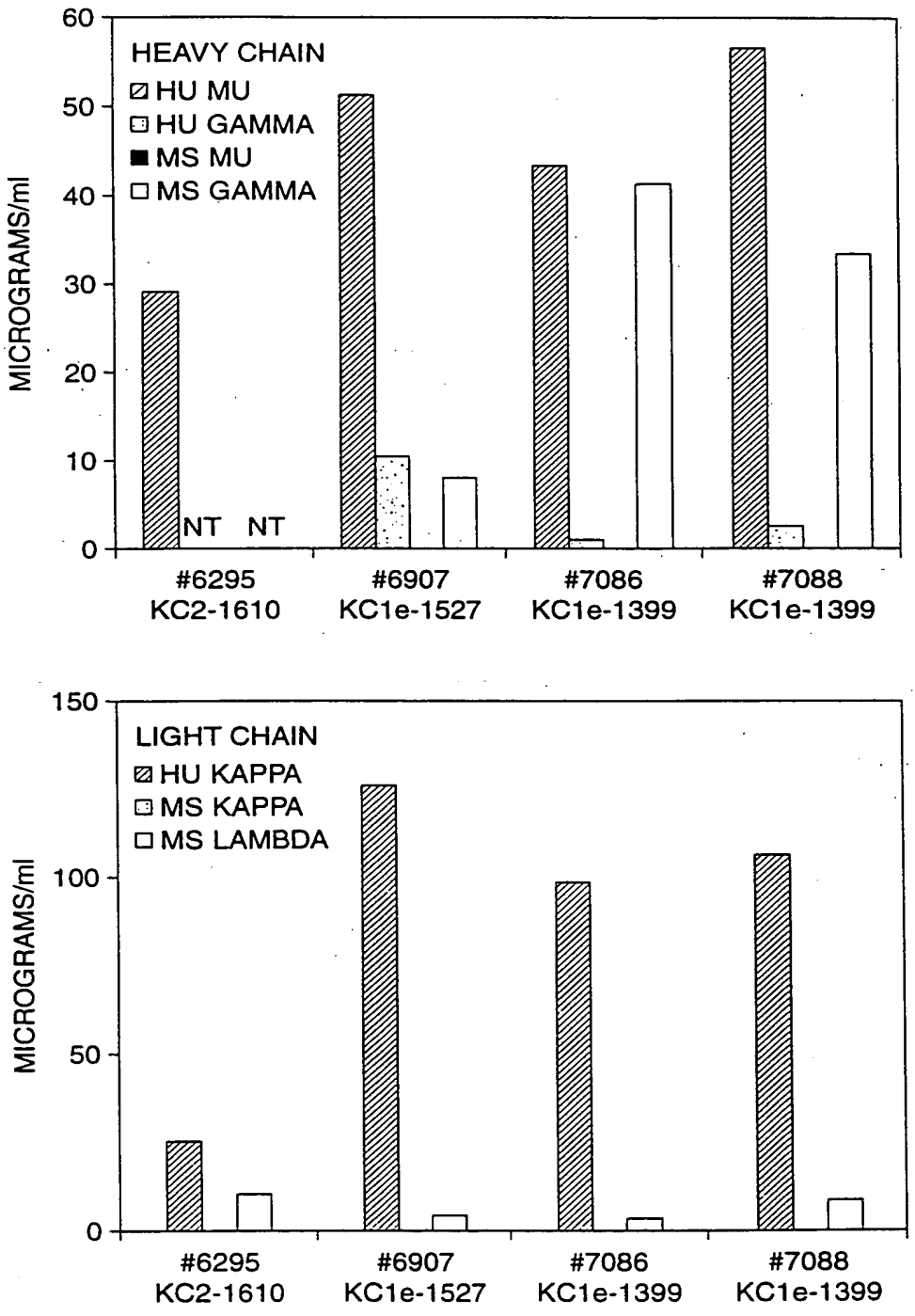

HEAVY CHAIN
HU MU
HU GAMMA
MS MU
MS GAMMA
MICROGRAMS/ml
60
50
40
30
20
10
0
NT NT
#6295
KC2-1610
#6907
KC1e-1527
#7086
KC1e-1399
#7088
KC1e-1399
LIGHT CHAIN
HU KAPPA
MS KAPPA
MS LAMBDA
MICROGRAMS/ml
150
100
50
0
#6295
KC2-1610
#6907
KC1e-1527
#7086
KC1e-1399
#7088
KC1e-1399

FIG. 53

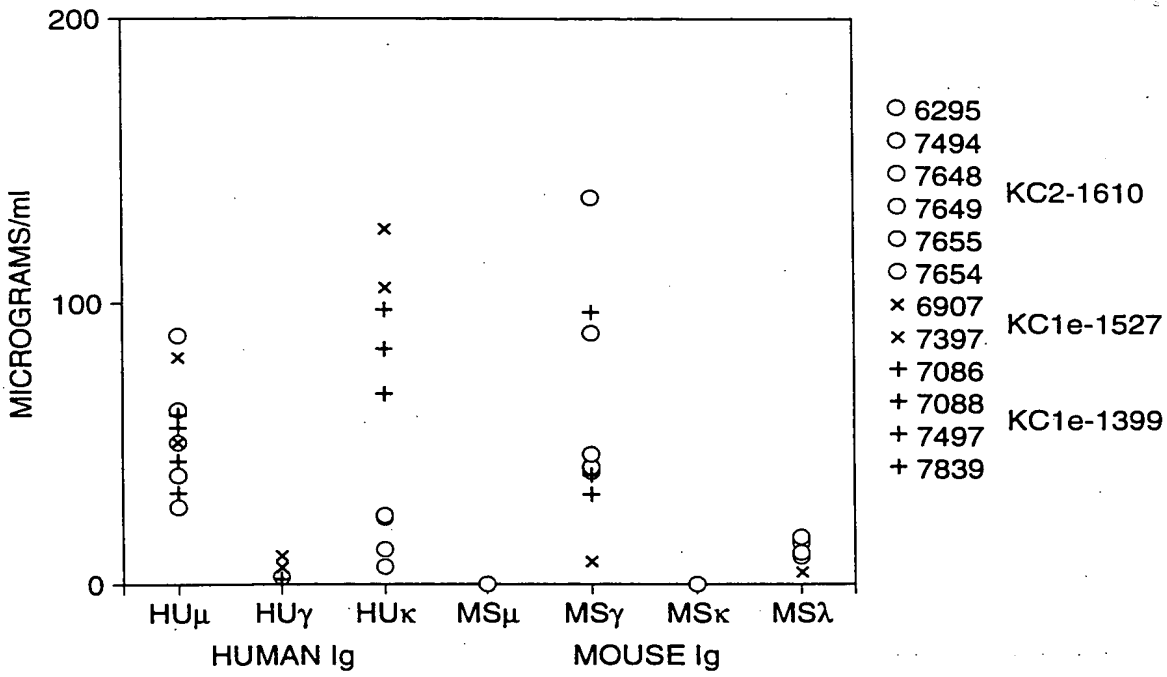

200
100
0
MICROGRAMS/ml
HUμ
HUγ
HUκ
MSμ
MSγ
MSκ
MSλ
HUMAN Ig
MOUSE Ig
○ 6295
○ 7494
○ 7648
○ 7649
○ 7655
○ 7654
KC2-1610
× 6907
× 7397
KC1e-1527
+ 7086
+ 7088
+ 7497
+ 7839
KC1e-1399

FIG. 54

Anti-human CD4 titers in 0011 mouse

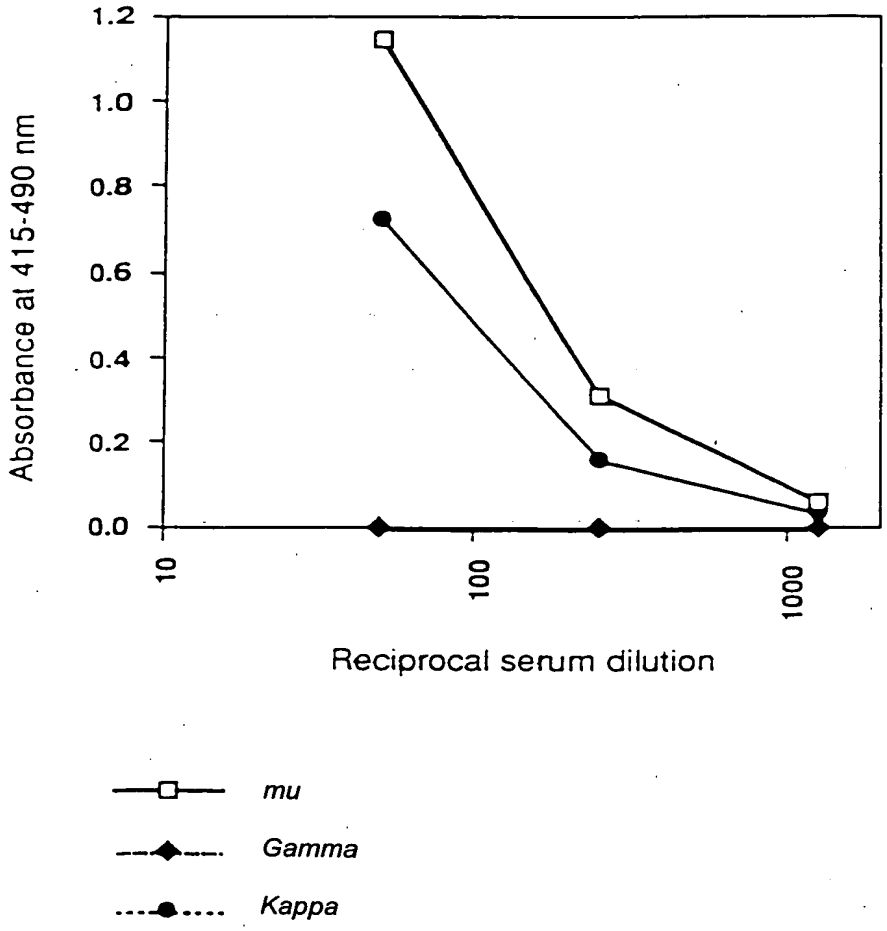
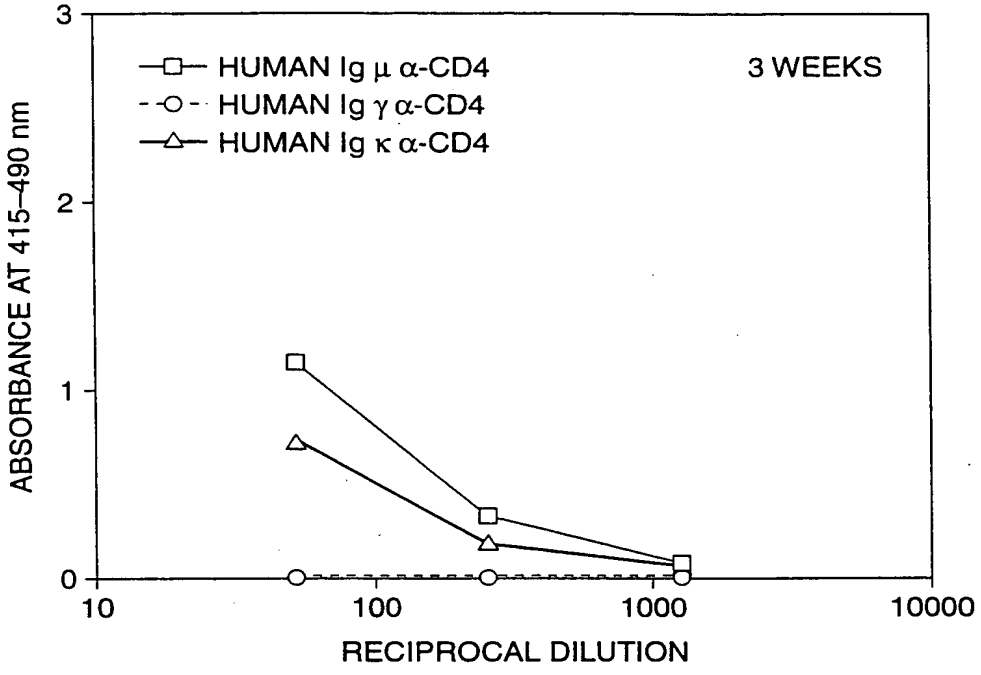


FIGURE 55


HUMAN Ig μ α-CD4
HUMAN Ig γ α-CD4
HUMAN Ig κ α-CD4
3 WEEKS
ABSORBANCE AT 415–490 nm
RECIPROCAL DILUTION
0
1
2
3
10
100
1000
10000

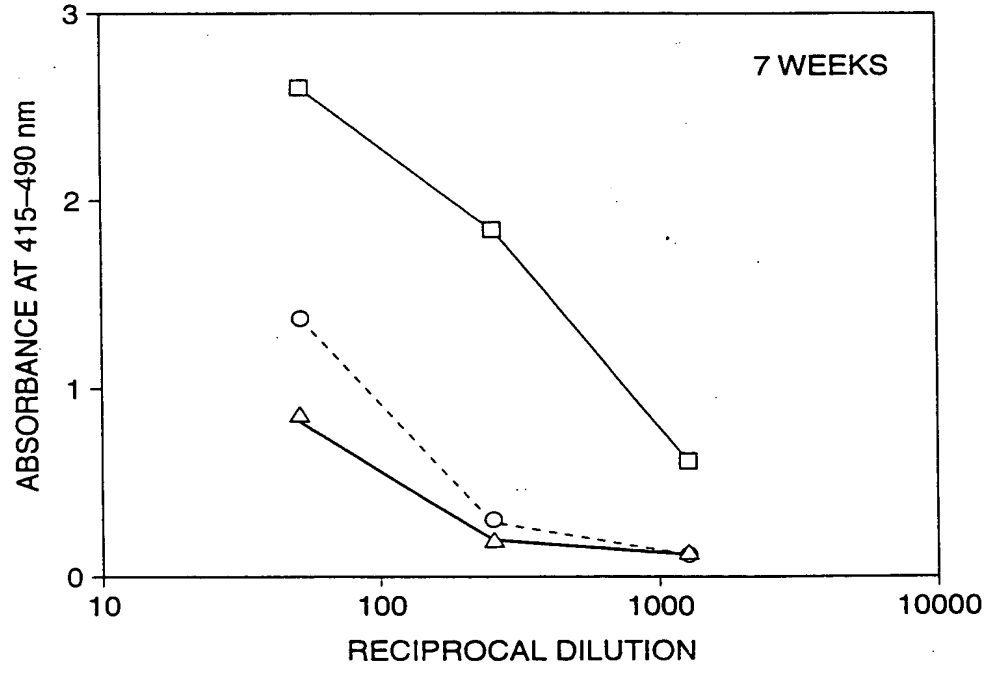

7 WEEKS
ABSORBANCE AT 415–490 nm
RECIPROCAL DILUTION
0
1
2
3
10
100
1000
10000

FIG. 56

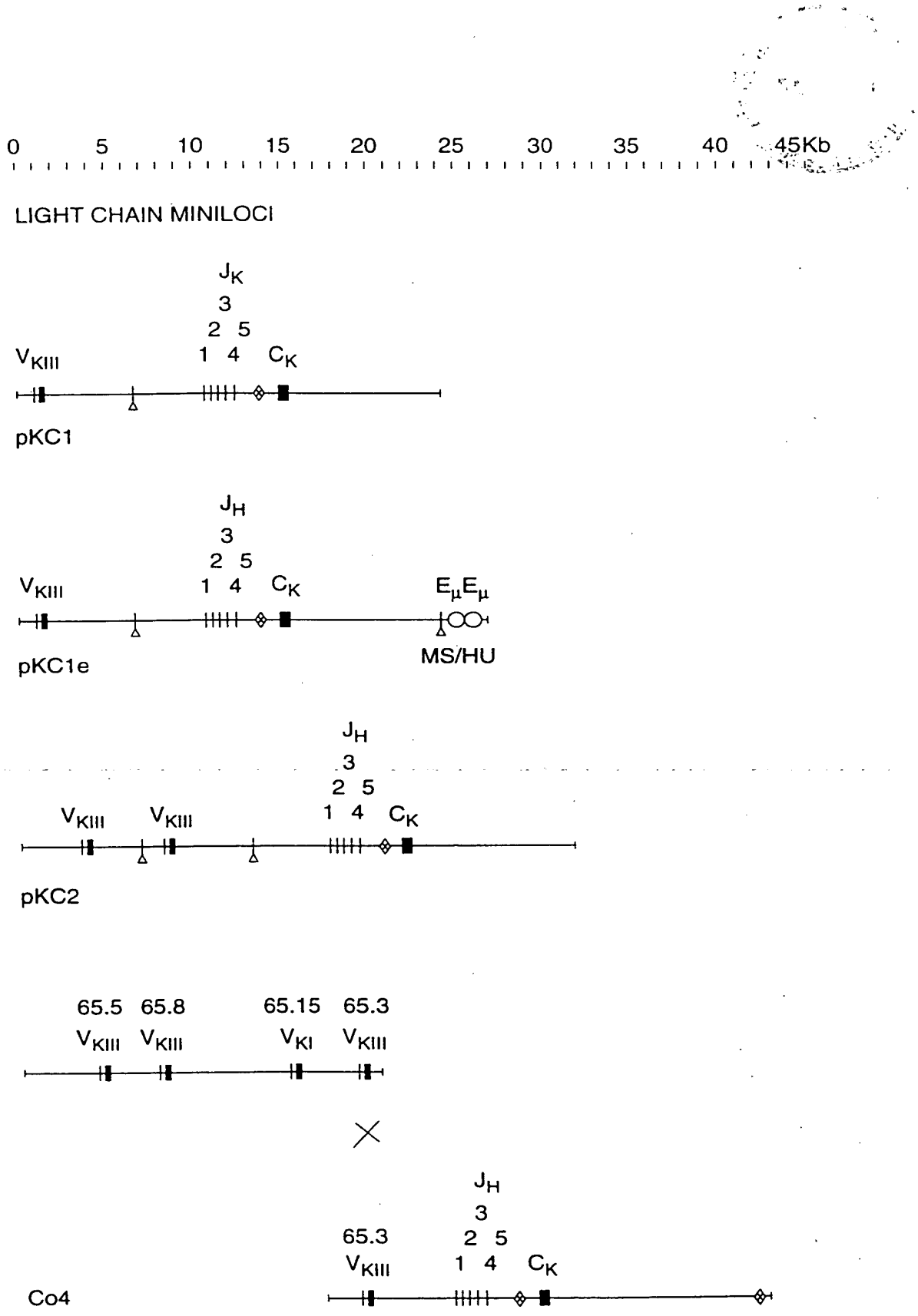

0 5 10 15 20 25 30 35 40 45Kb
LIGHT CHAIN MINILOCI
J_K
3
2 5
1 4
V_{KIII}
C_K
pKC1
J_H
3
2 5
1 4
V_{KIII}
C_K
$E_\mu E_\mu$
MS/HU
pKC1e
J_H
3
2 5
1 4
V_{KIII}
V_{KIII}
C_K
pKC2
65.5 65.8 65.15 65.3
V_{KIII} V_{KIII} V_{KI} V_{KIII}
J_H
3
2 5
1 4
65.3
V_{KIII}
C_K
Co4

FIG. 57A

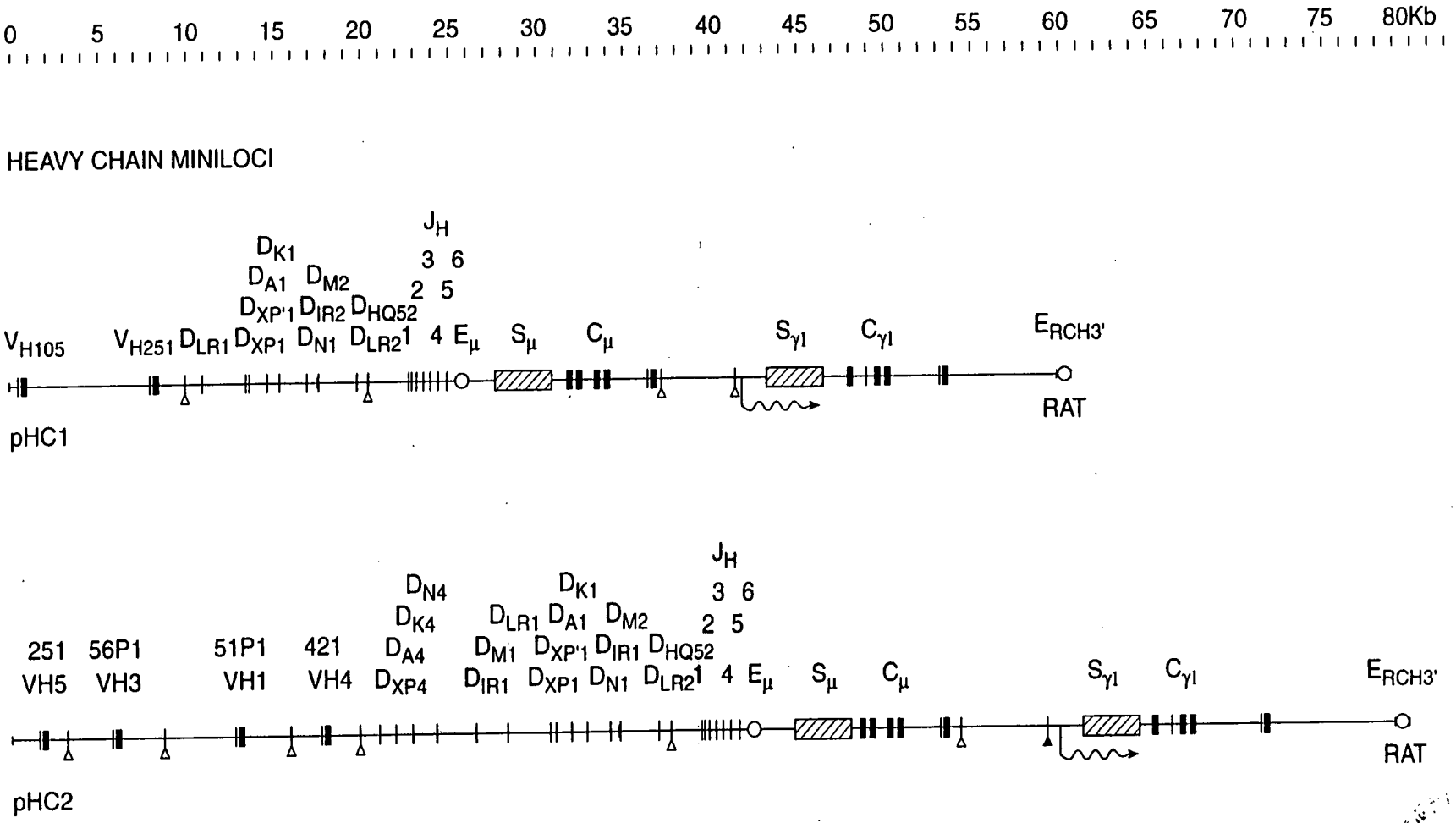

0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80Kb
HEAVY CHAIN MINILOCI
J_H
D_{K1}
3 6
D_{A1} D_{M2}
2 5
$D_{XP'1}$ D_{IR2} D_{HQ52}
V_{H105} V_{H251} D_{LR1} D_{XP1} D_{N1} D_{LR2} 1 4 E_μ S_μ C_μ $S_{\gamma 1}$ $C_{\gamma 1}$ $E_{RCH3'}$
RAT
pHC1
J_H
D_{N4} D_{K1}
3 6
D_{K4} D_{LR1} D_{A1} D_{M2}
2 5
251 56P1 51P1 421 D_{A4} D_{M1} $D_{XP'1}$ D_{IR1} D_{HQ52}
VH5 VH3 VH1 VH4 D_{XP4} D_{IR1} D_{XP1} D_{N1} D_{LR2} 1 4 E_μ S_μ C_μ $S_{\gamma 1}$ $C_{\gamma 1}$ $E_{RCH3'}$
RAT
pHC2

FIG. 57B

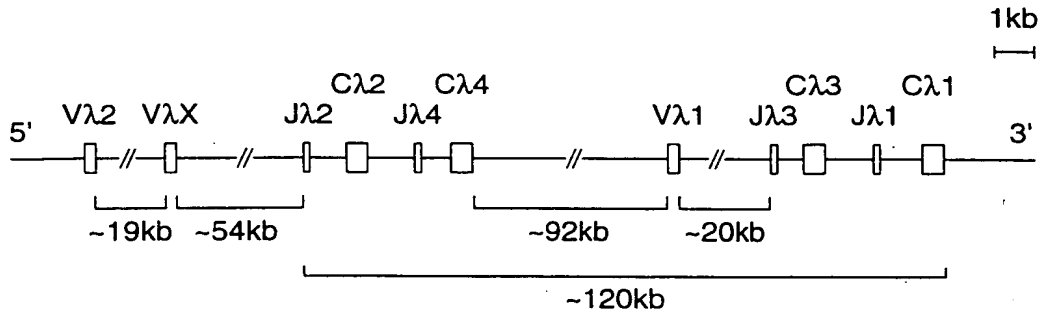

1kb
Cλ2
Cλ4
Cλ3
Cλ1
Vλ2
VλX
Jλ2
Jλ4
Vλ1
Jλ3
Jλ1
5'
3'
~19kb
~54kb
~92kb
~20kb
~120kb

FIG. 58

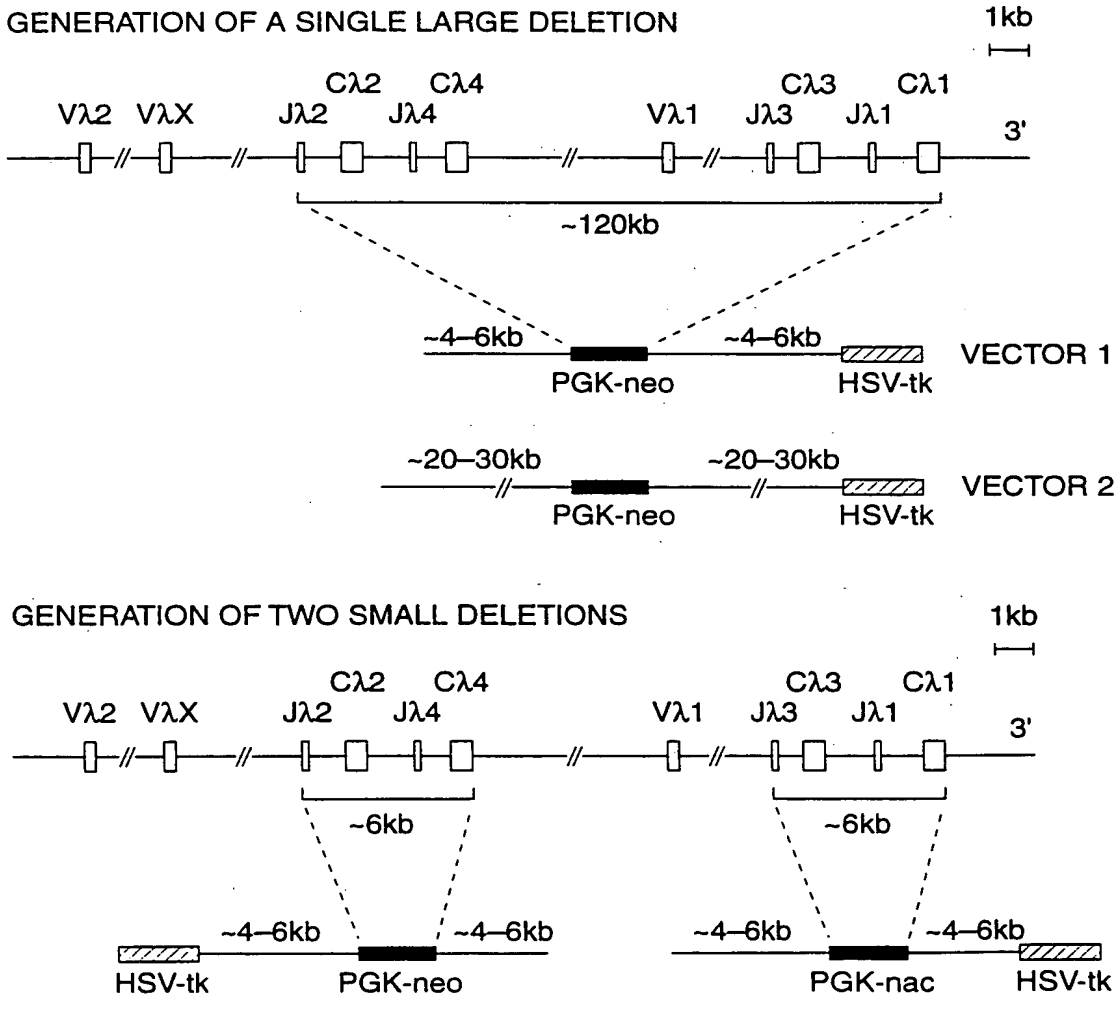

GENERATION OF A SINGLE LARGE DELETION
1kb
Cλ2
Cλ4
Cλ3
Cλ1
Vλ2
VλX
Jλ2
Jλ4
Vλ1
Jλ3
Jλ1
3'
~120kb
~4–6kb
~4–6kb
PGK-neo
HSV-tk
VECTOR 1
~20–30kb
~20–30kb
PGK-neo
HSV-tk
VECTOR 2
GENERATION OF TWO SMALL DELETIONS
1kb
Cλ2
Cλ4
Cλ3
Cλ1
Vλ2
VλX
Jλ2
Jλ4
Vλ1
Jλ3
Jλ1
3'
~6kb
~6kb
~4–6kb
~4–6kb
~4–6kb
~4–6kb
HSV-tk
PGK-neo
PGK-nac
HSV-tk

FIG. 59

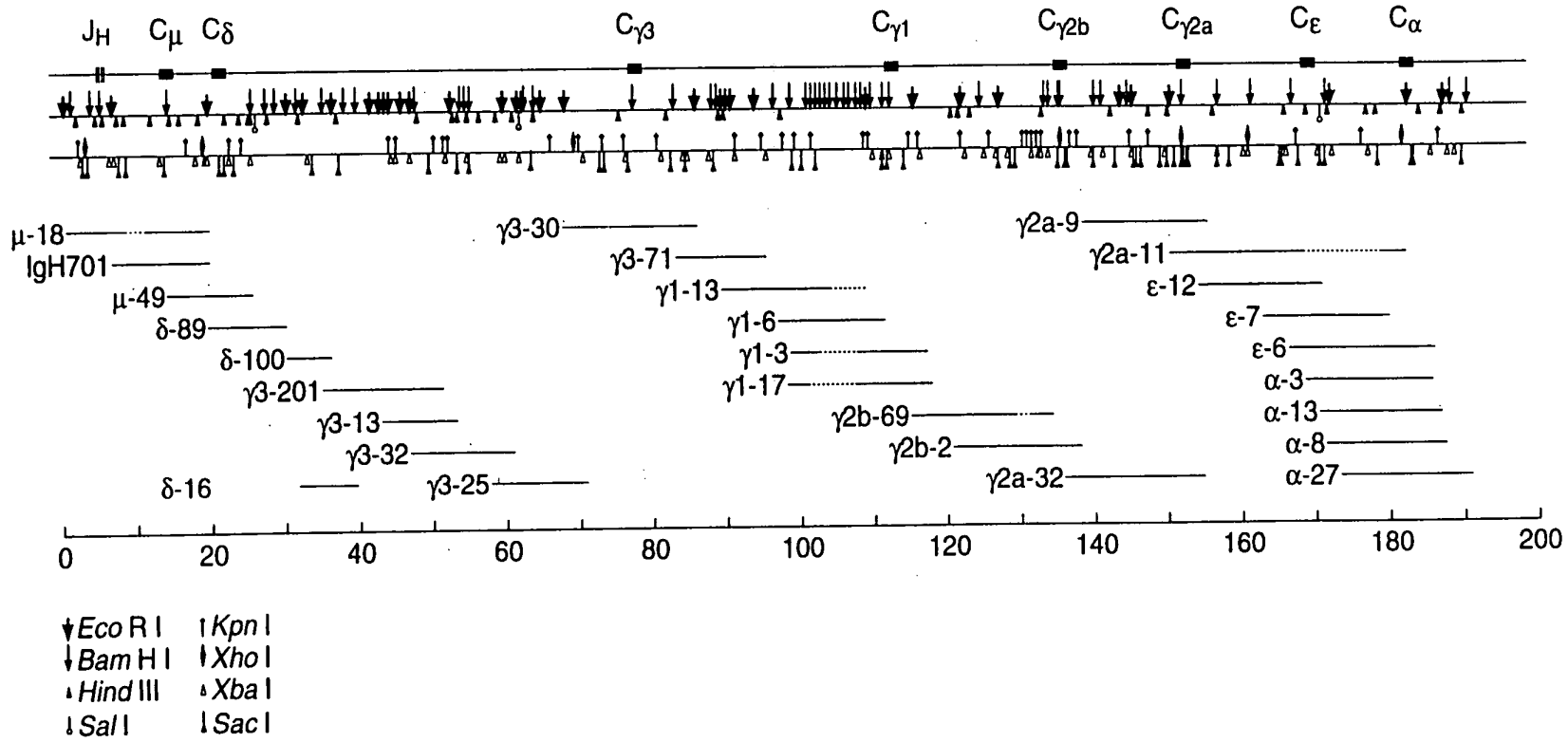

JH
Cμ
Cδ
Cγ3
Cγ1
Cγ2b
Cγ2a
Cε
Cα
μ-18
IgH701
μ-49
δ-89
δ-100
γ3-201
γ3-13
γ3-32
δ-16
γ3-25
γ3-30
γ3-71
γ1-13
γ1-6
γ1-3
γ1-17
γ2b-69
γ2b-2
γ2a-32
γ2a-9
γ2a-11
ε-12
ε-7
ε-6
α-3
α-13
α-8
α-27
0
20
40
60
80
100
120
140
160
180
200
Eco R I
Bam H I
Hind III
Sal I
Kpn I
Xho I
Xba I
Sac I

FIG. 60

CGAGAGGGGCGGGGGGAAGACTACTATCCCAGGCAGGTTTTAGGTTCCAGAGTCTGCGAG
AAATCCCACCATCTACCCACTGACACTCCCACCAGTCCTGTGCAGTGATCCCGTGATAAT
CGGCTGCCTGATTCACGATTACTTCCCTTTCGGCACGATGAATGTGACCTGGGGAAAGAG
TGGGAAGGATATAACCACCGTGAACTTTCCACCTGCCCTCGCCTCTGGGGGACGGTACAC
CATGAGCAGCCAGTTAACCCTGCCAGCTGTCGAGTGCCCAGAAGGAGAGTCCGTGAAATG
TTCCGTGCAACATGACTCTAACCCCGTCCAAGAATTGGATGTGAATTGCTCTGGTAAAGA
ACGTTAGGGGGTCAGCTAGGGGTGGGATAAGTCCTACCTTATCTAGATCCATATATCCCT
CTGATGCACACCCTCACAGGAATCCCTCAGAAACCTCCACTATGGGGATTGGGGGAAGGA
AGCGTAAACAGGTCTAGAAGGAGCTGGAGGCCTCAGAACATCCAGAAACGGGGACAGCAA
AGGAGACAAGGAGAATATACTGATTTGCTAGGACATCTTCTGTTACAGGTCCTACTCCTC
CTCCTCCTATTACTATTCCTTCCTGCCAGCCCAGCCTGTCACTGCAGCGGCCAGCTCTTG
AGGACCTGCTCCTGGGTTCAGATGCCAGCATCACATGTACTCTGAATGGCCTGAGAAATC
CTGAGGGAGCTGCTTTCACCTGGGAGCCCTCCACTGGGAAGGATGCAGTGCAGAAGAAAG
CTGCGCAGAATTCCTGCGGCTGCTACAGTGTGTCCAGCGTCCTGCCTGGCTGTGCTGAGC
GCTGGAACAGTGGCGCATCATTCAAGTGCACAGTTACCCATCCTGAGTCTGGCACCTTAA
CTGGCACAATTGCCAAAGTCACAGGTGAGCTCAGATGCATACCAGGACATTGTATGACGT
TCCCTGCTCACATGCCTGCTTTCTTCCTATAATACAGATGCTCAACTAACTGCTCATGTC
CTTATATCACAGAGGGAAATTGGAGCTATCTGAGGAACTGCCCAGAAGGGAAGGGCAGAG
GGGTCTTGCTCTCCTTGTCTGAGCCATAACTCTTCTTTCTACCTTCCAGTGAACACCTTC
CCACCCCAGGTCCACCTGCTACCGCCGCCGTCGGAGGAGCTGGCCCTGAATGAGCTCTTG
TCCCTGACATGCCTGGTGCGAGCTTTCAACCCTAAAGAAGTGCTGGTGCGATGGCTGCAT
GGAAATGAGGAGCTGTCCCCAGAAAGCTACCTAGTGTTTGAGCCCCTAAAGGAGCCAGGC
GAGGGAGCCACCACCTACCTGGTGACAAGCGTGTTGCGTGTATCAGCTGAAACCTGGAAA
CAGGGTGACCAGTACTCCTGCATGGTGGGCCACGAGGCCTTGCCCATGAACTTCACCCAG
AAGACCATCGACCGTCTGTCGGGTAAACCCACCAATGTCAGCGTGTCTGTGATCATGTCA
GAGGGAGATGGCATCTGCTACTGAGCCACCCTGCCTGTCCCTACTCCTAGAATAAACTCT
GTGCTCATCCAAAGTATCCCTGCACTTCCACCCAGTGCCTGTCCACCACCCTGGGGTCTA
CGAAACACAGGGAGGGGTCAGGGCCCAGGGAGGGAGAAATACCACCACCTAAGC

FIG. 61

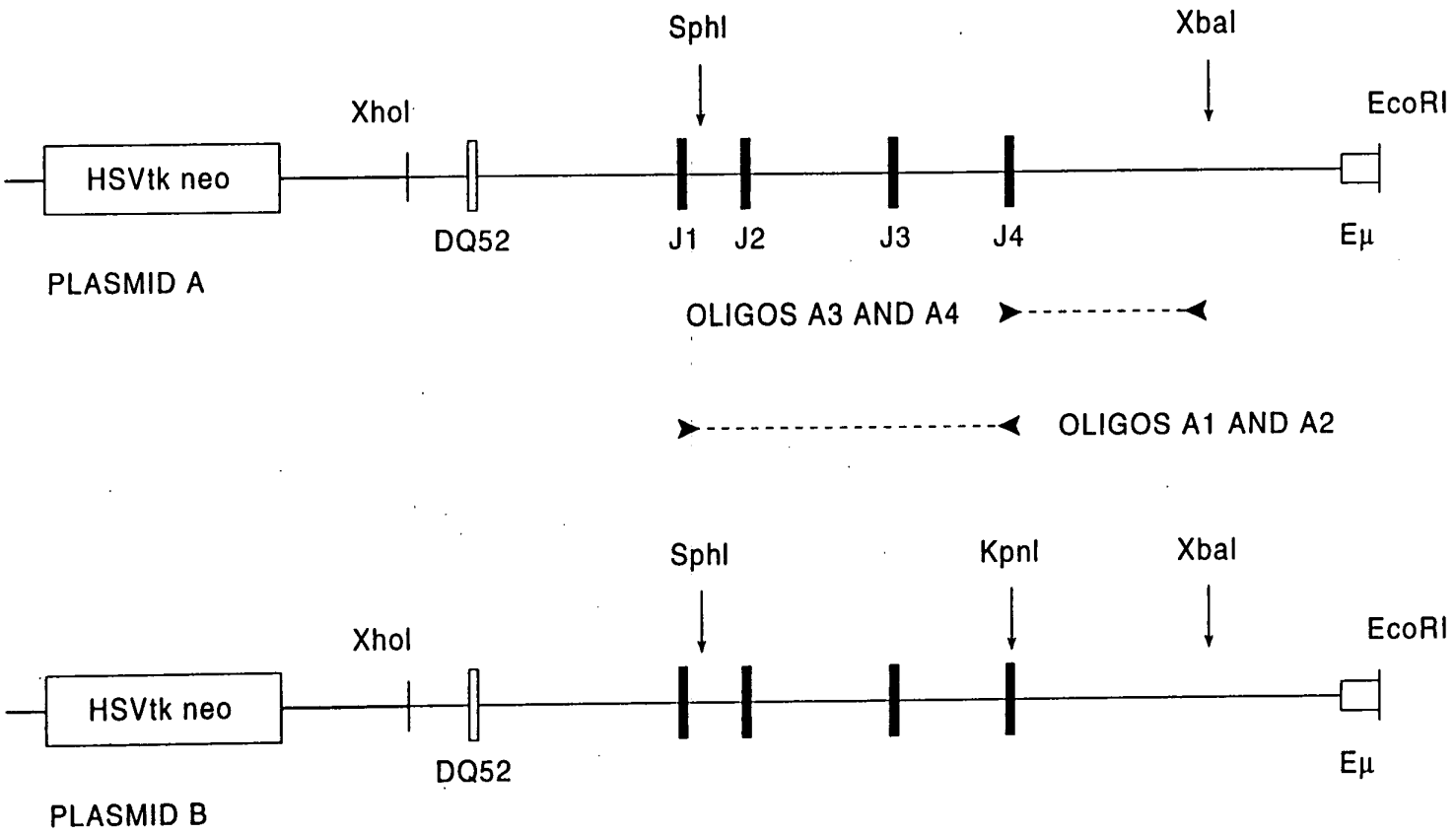

SphI
XbaI
XhoI
EcoRI
HSVtk neo
DQ52
J1
J2
J3
J4
Eμ
PLASMID A
OLIGOS A3 AND A4
OLIGOS A1 AND A2
SphI
KpnI
XbaI
XhoI
EcoRI
HSVtk neo
DQ52
Eμ
PLASMID B

FIG. 62

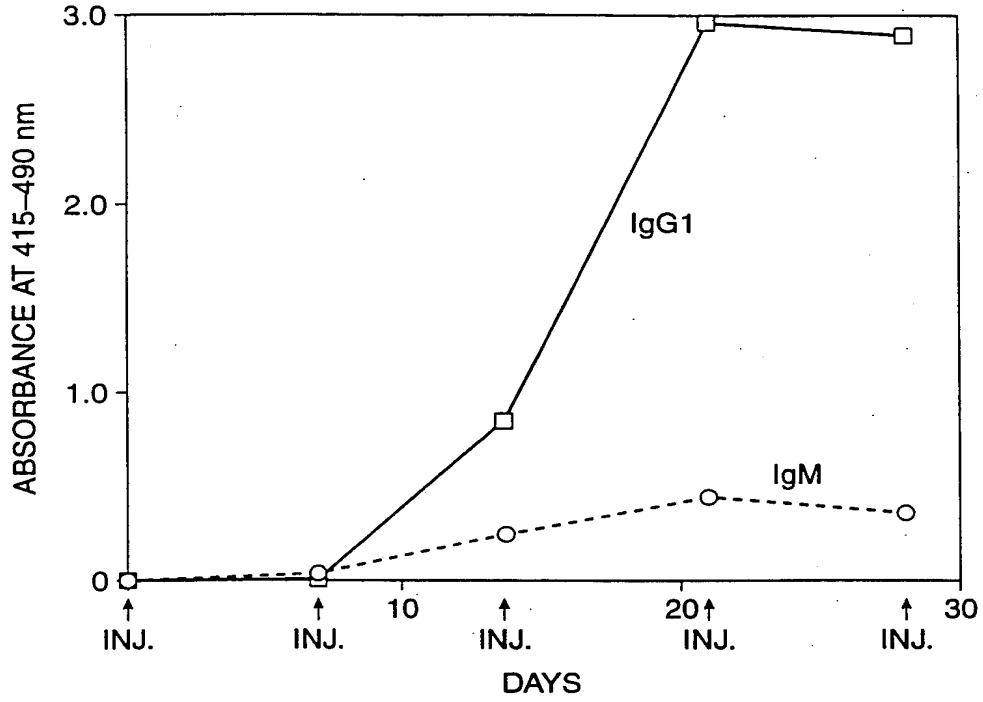

3.0
2.0
1.0
0
ABSORBANCE AT 415–490 nm
IgG1
IgM
10
20
30
INJ.
INJ.
INJ.
INJ.
INJ.
DAYS

FIG. 63

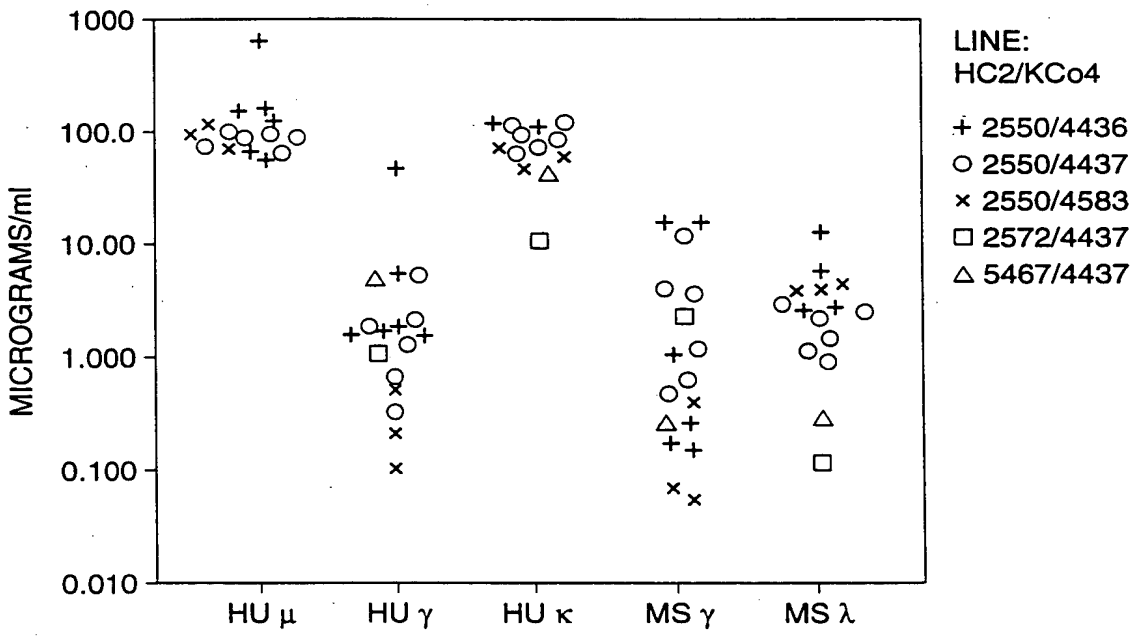

1000
100.0
10.00
1.000
0.100
0.010
MICROGRAMS/ml
HU μ
HU γ
HU κ
MS γ
MS λ
LINE:
HC2/KCo4
+ 2550/4436
○ 2550/4437
× 2550/4583
□ 2572/4437
△ 5467/4437

FIG. 70

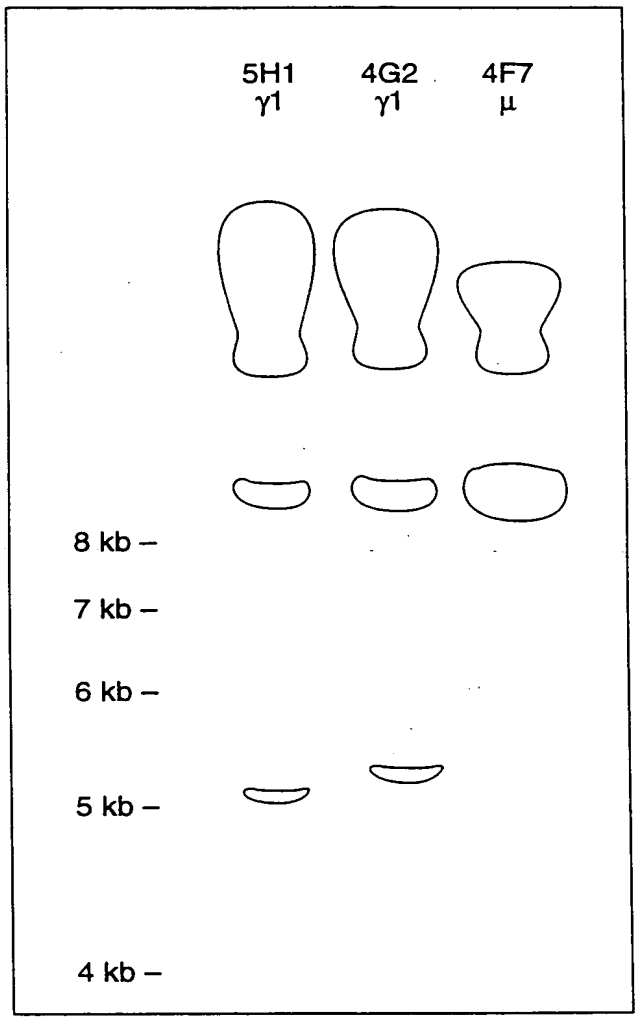


FIG. 64A

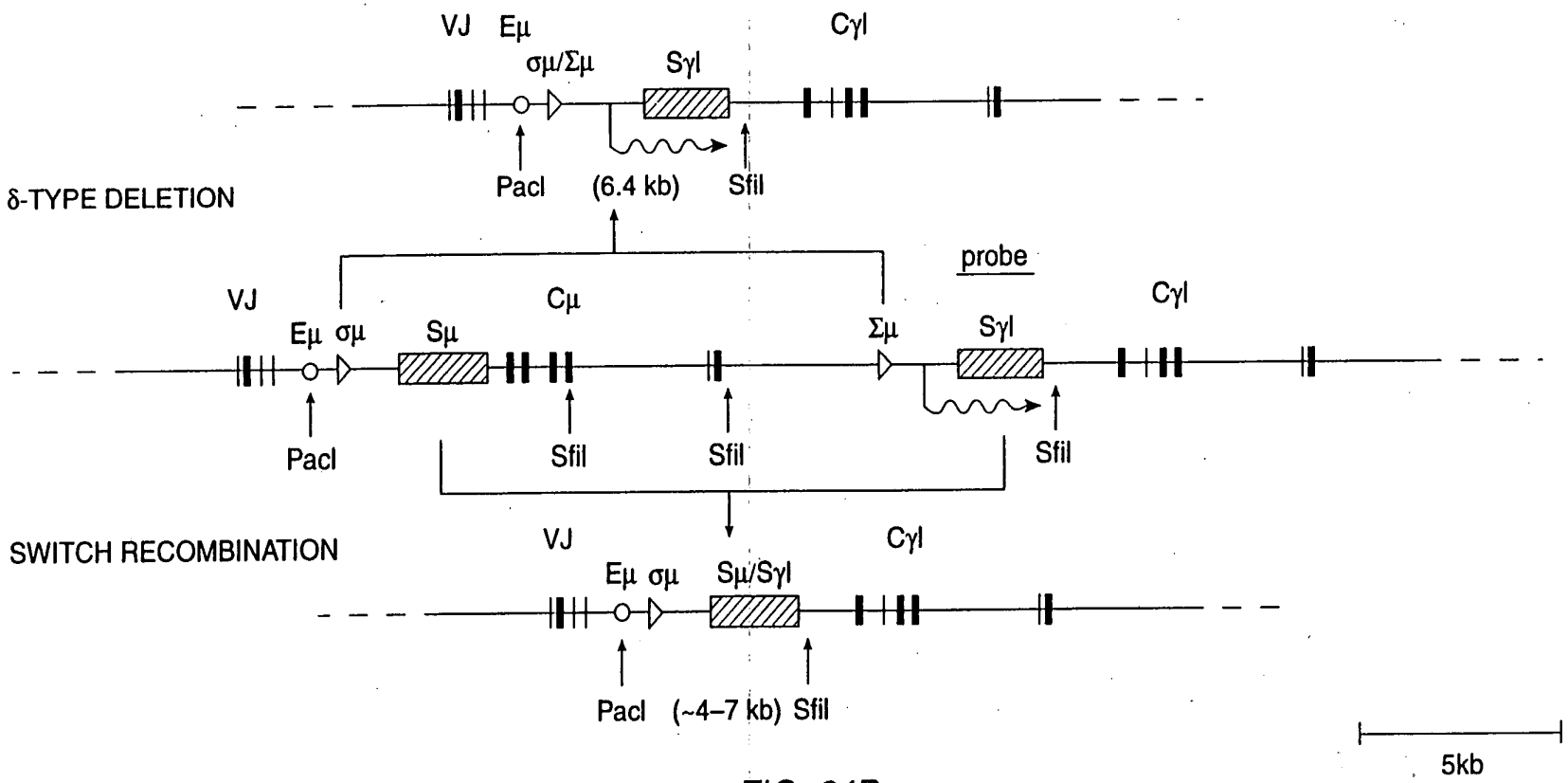

VJ
Eμ
σμ/Σμ
Sγl
Cγl
PacI
(6.4 kb)
SfiI
δ-TYPE DELETION
probe
VJ
Cμ
Cγl
Eμ
σμ
Sμ
Σμ
Sγl
PacI
SfiI
SfiI
SfiI
SWITCH RECOMBINATION
VJ
Cγl
Eμ
σμ
Sμ/Sγl
PacI
(~4–7 kb)
SfiI
5kb

FIG. 64B

	V_H251	N D N	J	$C\gamma$
				mouse γ1
2357.t5 DXP'1 J6	gcctcggacaccgccatgtattactgtgTgaga	CATTtatggttcggggagttaCG	cggtGtgAacgtctggggccaagggaccacggtcaccgtctcctcag	ccaaaacgacacccccatctgtctatccac
2357.t7 DHQ52 J3	gcctcggacaccgccatgtattactgtgcgaga	CactgggCATTGGAT	gctCttgatGtctggggccaagggacaatgCtcaccgtctcttcag	ccaaaacgacacccccatctgtctatccac
				mouse γ2b
2357.t2 DHQ52 J3	gcctcggacaccgccatgtattactgtgcgaga	actggggaTGAT	gcttttgatatctggggccaagggacaatggtcaccgtctcttcag	ccaaaacaacacccccatcagtctatccac
2357.t3 D? J3	gActcggacaccgccatgtattactgtgcgaga	CAGGGGAGAGAT	gctttagatatctggggccaagggacaatggtcaccgtctcttcag	ccaaaacaacacccccatcagtctatccac
2357.t4 DXP'1 J4	gcctcggacaccgccatgtattaTtgtgTgaga	CATAGGGactatATttcggggagttattTTCC	tgactactggggccagggaaccctggtcaccgtctcctcag	ccaaaacaacacccccatcagtctatccac
2357.t10 DHQ52 J3	gcctcggacaccgccatgtattactgtgcgaga	actggggaTGAT	gcttttgatatctggggccaagggacaatggtcaccgtctcttcag	ccaaaacaacacccccatcagtctatccac
				mouse γ3
2357.t1 D? J3	gcctcggacaccgccatgtattactgtgcgaga	CATGGGTCTATG	gatatctggggccaagggacaatggtcaccgtctcttcag	ctacaacaacagccccatctgtctatccct
2357.t6 DHQ52 J4	gcctcggacaccgccatgtattactgtgcgaga	GAGAGCGGTCactggggaTCG	tttgactaTtggggccagggaaccctggtcaccgtctcctcag	ctacaacaacagccccatctgtctatccct
2357.t8 DIR2 J3	gcctcggacaccgccatgtattactgtgcgaga	AGGgacccccCTGAT	gcttttgatatctggggccaagggacaatggtcaccgtctcttcag	ctacaacaacagccccatctgtctatccct
2357.t9 DIR2R J6	gcctcggacaccgccatgtattactgtgcgaga	CGggggcct	tactactactacggtatggacgtctggggccaagggaccacggtcaccgtctcctcag	ctacaacaacagccccatctgtctatccct
			human	mouse

FIG. 65

```
                  20                            30                            40                            50    52 a  53                60
VH251.GL  TCTCTGAAGATCTCCTGTAAGGGTTCTGGATACAGCTTTACCAGCTACTGGATCGGCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGGGGATCATCTATCCTGGTGACTCTGATACCAGATACAGCCCGTCCTTCCAAGGCCAGGTC
J2
2599.7    ............................................................................................................................................................
2599.9    ............................................................................................................................................................
2599.11   ............................................................................................................................................................
2599.14   ............................................................................................................................................................
J3
2599.25   .............................................................C..............................................................................................
J4
2599.2    ............................................................................................................................................................
2599.5    ............................................................................................................................................................
2599.8    ............................................................................................................................................................
2599.23   ............................................................................................................................................................
2599.24   ............................................................................................................................................................
2599.28   ............................................................................................................................................................
J6
2599.10   ............................................................................................................................................................
2599.13   ............................................................................................................................................................
                                        ________________                                                     ______________________________________________
                                             CDR I                                                                               CDR II
```

FIG. 66A-1

```
   70                                     80     82 a  b  c  83                                  90
ACCATCTCAGCCGACAAGTCCATCAGCACCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCTCGGACACCGCCATGTATTACTGTGCGAGA
                                                                                                                                 TACTGGTACTTCGATCTCTGGGGCCGTGGCAC
.......................................................................................... CAAGGGactggggaGG             ................................ DHQ52
.......................................................................................... CAGAAGGGGGGAAGGG                ............................
.......................................................................................... CAGAAGGGGGGAAGGG                ............................
.......................................................................................... actgggTGG                  ................................ DHQ52
                                                                                                                                       GCTTTTGATATCTGGGGCCAAGGGAC
.......................................................................................... CATGAaactggggaTCCGGGG                  ......................... DHQ52
                                                                                                                                       TACTTTGACTACTGGGGCCAGGGAAC
.......................................................................................... ACGGattacgatattttgactggttattataacCCT         ....................... DXP1
.......................................................................................... tatagcagcagcCCTT                            ....................... DN1
.......................................................................................... TCTCtactatggttcggggag                       ....................... DXP'1
.......................................................................................... CTCGattacgatattttgactggttattataacCC          ........................ DXP1
.......................................................................................... CTCGattacgatattttgactggttattataacCC          ........................ DXP1
........G................................................................................. CCCgtatagcagcagctggtacAGG                   ....................... DN1
                                                                                                                         TACTACTACTACTACGGTATGGACGTCTGGGGCCAAGGGAC
.......................................................................................... GAGGGGGGGGTTtattactatggttcggggagttatta ................................ DXP'1
.......................................................................................... GAGGGaactggggaCCAT             ....G.................................. DHQ52
                                                                                           ________________________________________________________
                                                                                                          CDR III
```

FIG. 66A-2

```
                20                            30                           40                            50   52 a 53          60
VH251.GL   TCTCTGAAGATCTCCTGTAAGGGTTCTGGATACAGCTTTACCAGCTACTGGATCGGCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGGGGATCATCTATCCTGGTGACTCTGATACCAGATACAGCCCGTCCTTCCAAGGCCAGGTC
J2
3204.sp28  ..................................CGT.....................................................................................................
J3
3204.ln10  ..............................G...........................................................................................................
J4
3204.ln3   ......................................G...........................A.......................................................................
3204.ln7   ...............................A...C..G...........................A.......................................................................
3204.ln8   ......................................G...........................A.......................................................................
3204.ln14  .............................................................................................................................................
3204.ln15  ......................................G...........................A.......................................................................
3204.sp22  ................................T......................................C.................................................G.............
3204.sp26  ......................................G...........................A.......................................................................
3204.sp27  ....................................T........................................................................................................
3204.sp30  ......................................G...........................A.......................................................................
J5
3204.sp19  ...................T..........A....G.....................................................CA............................................
J6
3204.sp20  .............................T..T...G...A....G...................................................................C.G.T.......................
                                          ______________                                             _________________________________
                                              CDR I                                                              CDR II
```

FIG. 66B-1

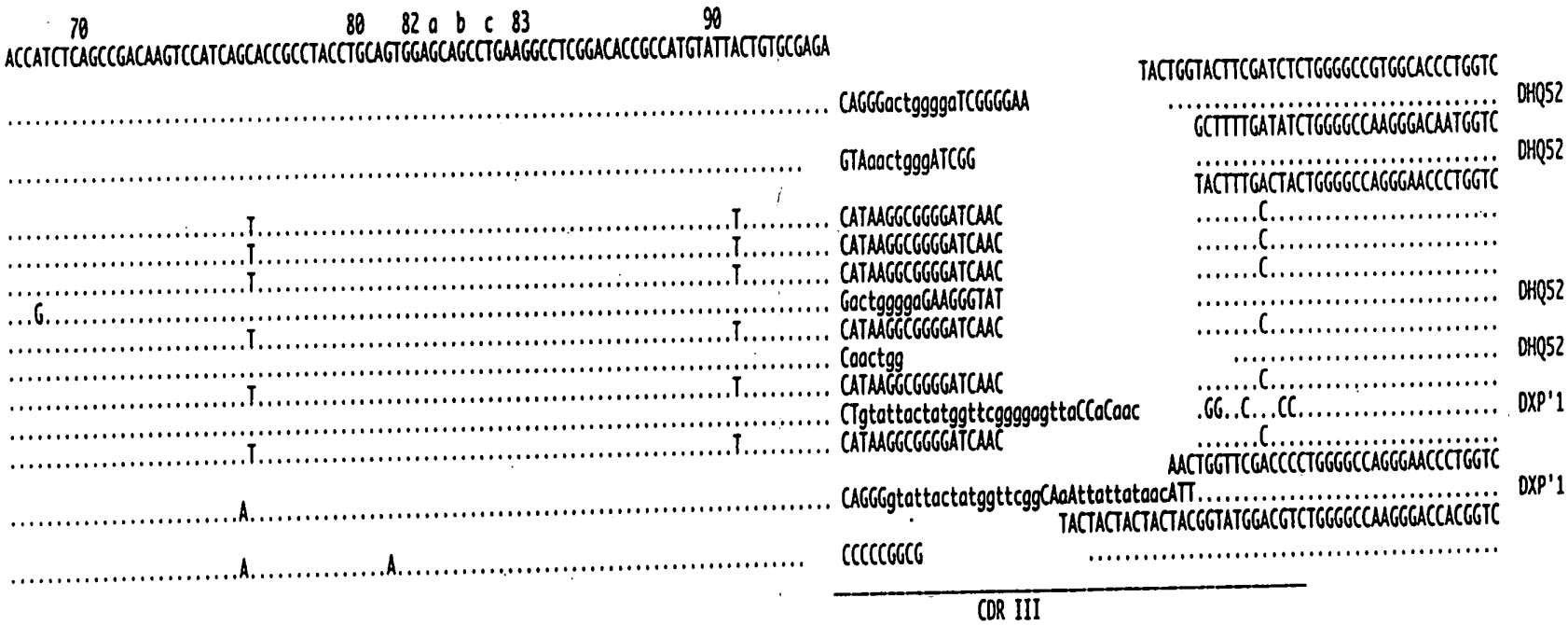


FIG. 66B-2

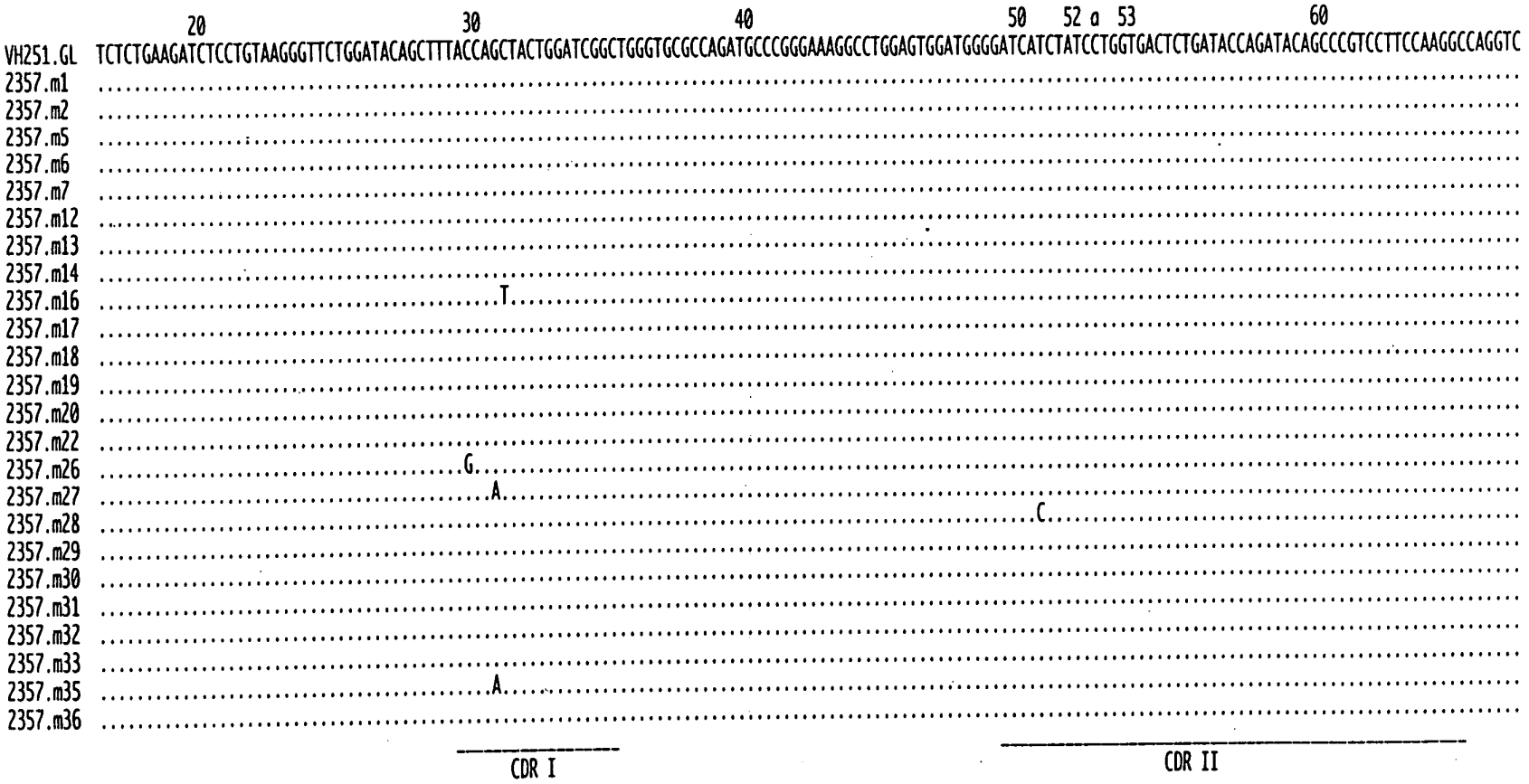

20
30
40
50
52 a
53
60
VH251.GL TCTCTGAAGATCTCCTGTAAGGGTTCTGGATACAGCTTTACCAGCTACTGGATCGGCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGGGGATCATCTATCCTGGTGACTCTGATACCAGATACAGCCCGTCCTTCCAAGGCCAGGTC
2357.m1
2357.m2
2357.m5
2357.m6
2357.m7
2357.m12
2357.m13
2357.m14
2357.m16 T
2357.m17
2357.m18
2357.m19
2357.m20
2357.m22
2357.m26 G
2357.m27 A
2357.m28 C
2357.m29
2357.m30
2357.m31
2357.m32
2357.m33
2357.m35 A
2357.m36
CDR I
CDR II

FIG. 67A

```
                    20                            30                            40                            50   52 a 53                     60
VH251.GL  TCTCTGAAGATCTCCTGTAAGGGTTCTGGATACAGCTTTACCAGCTACTGGATCGGCTGGGTGCGCCAGATGCCCGGGAAAGGCCTGGAGTGGATGGGGATCATCTATCCTGGTGACTCTGATACCAGATACAGCCCGTCCTTCCAAGGCCAGGTC
J2
2357.g5   .......................C..........................................................................................................................G.........
J3
2357.g10  ............................................................................................................................................................
2357.g24  ............................................................................................................................................................
J4
2357.g1   ...................................T...T..GA..............................................................................C.......................G.........
2357.g2   ............................................................................................................................................................
2357.g3   ..........................................................................................................GG................................................
2357.g4   .............................................C.A............................................................................................................
2357.g6   ...................................T...G....................................................................................................................
2357.g11  ...........................................A................................................................................................................
2357.g17  ..........................................................................................................................A...........T.....................
2357.g19  ...................G...................T....T..........C....................................................................................................
2357.g23  ............................................................................................................................................................
2357.g27  ............................................................................................................................................................
2357.g30  ............................................................................................................................................................
2357.g32  .......................................C...T................................................................................................................
2357.g34  ......................T...............A.....T..T............................................................................................................
2357.g36  ............................................................................................................................................................
J5
2357.g25  ..................................A........C................................................................................................................
2357.g35  ............................................................................................................................................................
J6
2357.g18  ..................................A.....T..C...........................A....................................................................................
2357.g22  ..................................C.........T..........C..................................................T.................................................
2357.g28  .......................................G...A..............................................................T...............................C.................
2357.g33  ............................................................................................................................................................
                                         ______________                                                      _____________________________
                                             CDR I                                                                       CDR II
```

FIG. 67B-1

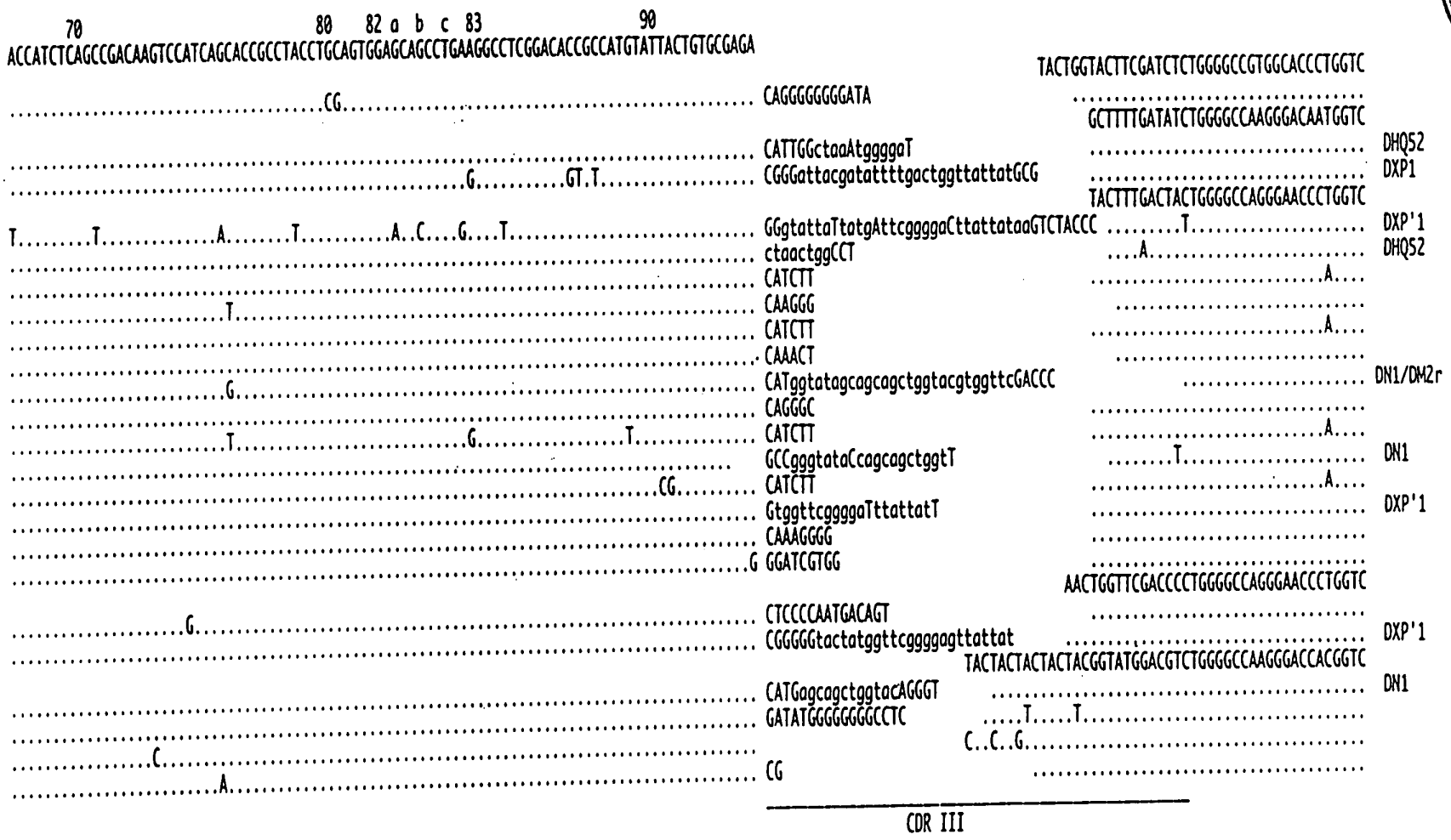


FIG. 67B-2

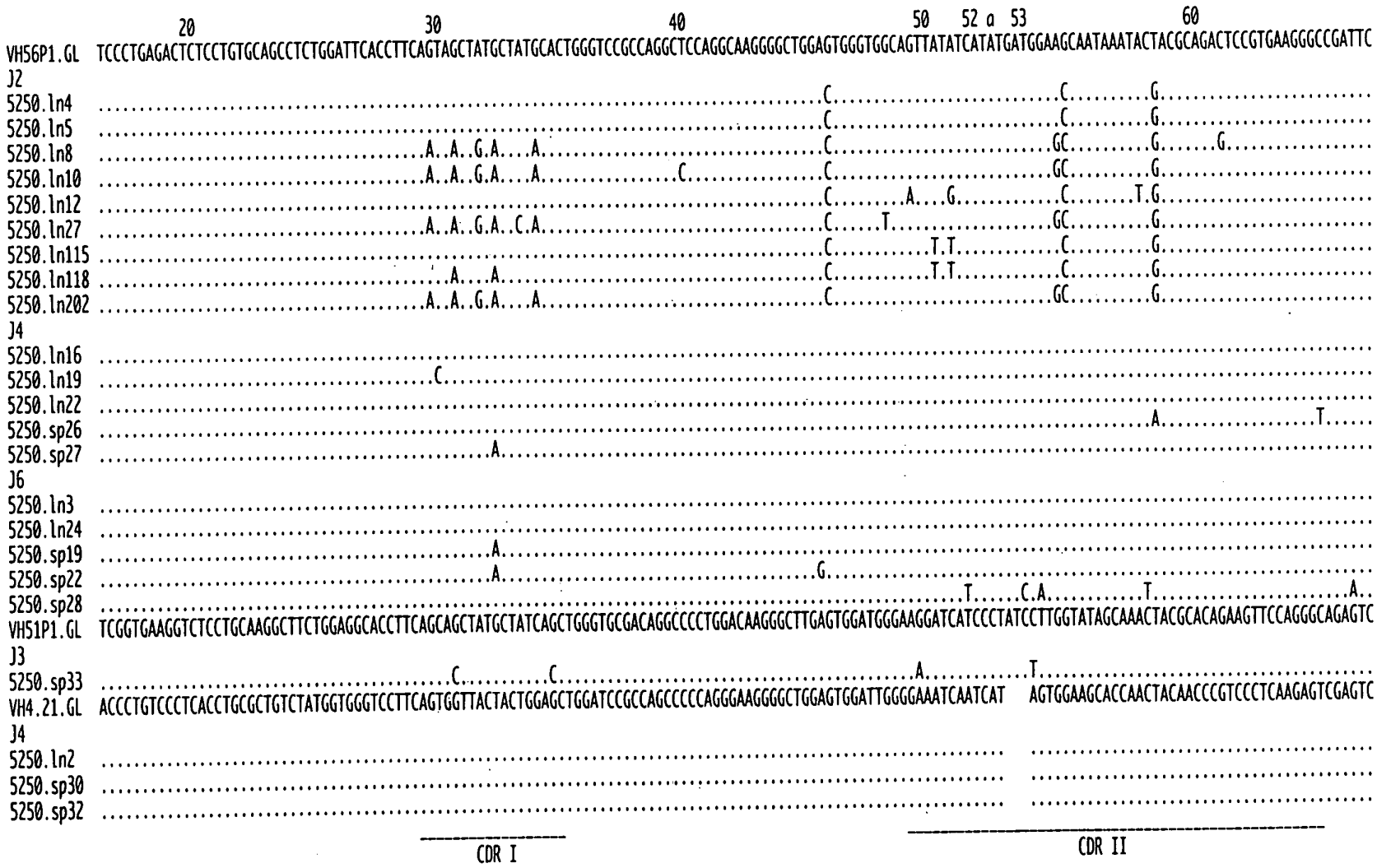

20
30
40
50
52 a
53
60
VH56P1.GL TCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGCTATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGCAATAAATACTACGCAGACTCCGTGAAGGGCCGATTC
J2
5250.ln4
5250.ln5
5250.ln8
5250.ln10
5250.ln12
5250.ln27
5250.ln115
5250.ln118
5250.ln202
J4
5250.ln16
5250.ln19
5250.ln22
5250.sp26
5250.sp27
J6
5250.ln3
5250.ln24
5250.sp19
5250.sp22
5250.sp28
VH51P1.GL TCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTATCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAAGGATCATCCCTATCCTTGGTATAGCAAACTACGCACAGAAGTTCCAGGGCAGAGTC
J3
5250.sp33
VH4.21.GL ACCCTGTCCCTCACCTGCGCTGTCTATGGTGGGTCCTTCAGTGGTTACTACTGGAGCTGGATCCGCCAGCCCCCAGGGAAGGGGCTGGAGTGGATTGGGGAAATCAATCAT AGTGGAAGCACCAACTACAACCCGTCCCTCAAGAGTCGAGTC
J4
5250.ln2
5250.sp30
5250.sp32
CDR I
CDR II

FIG. 68A

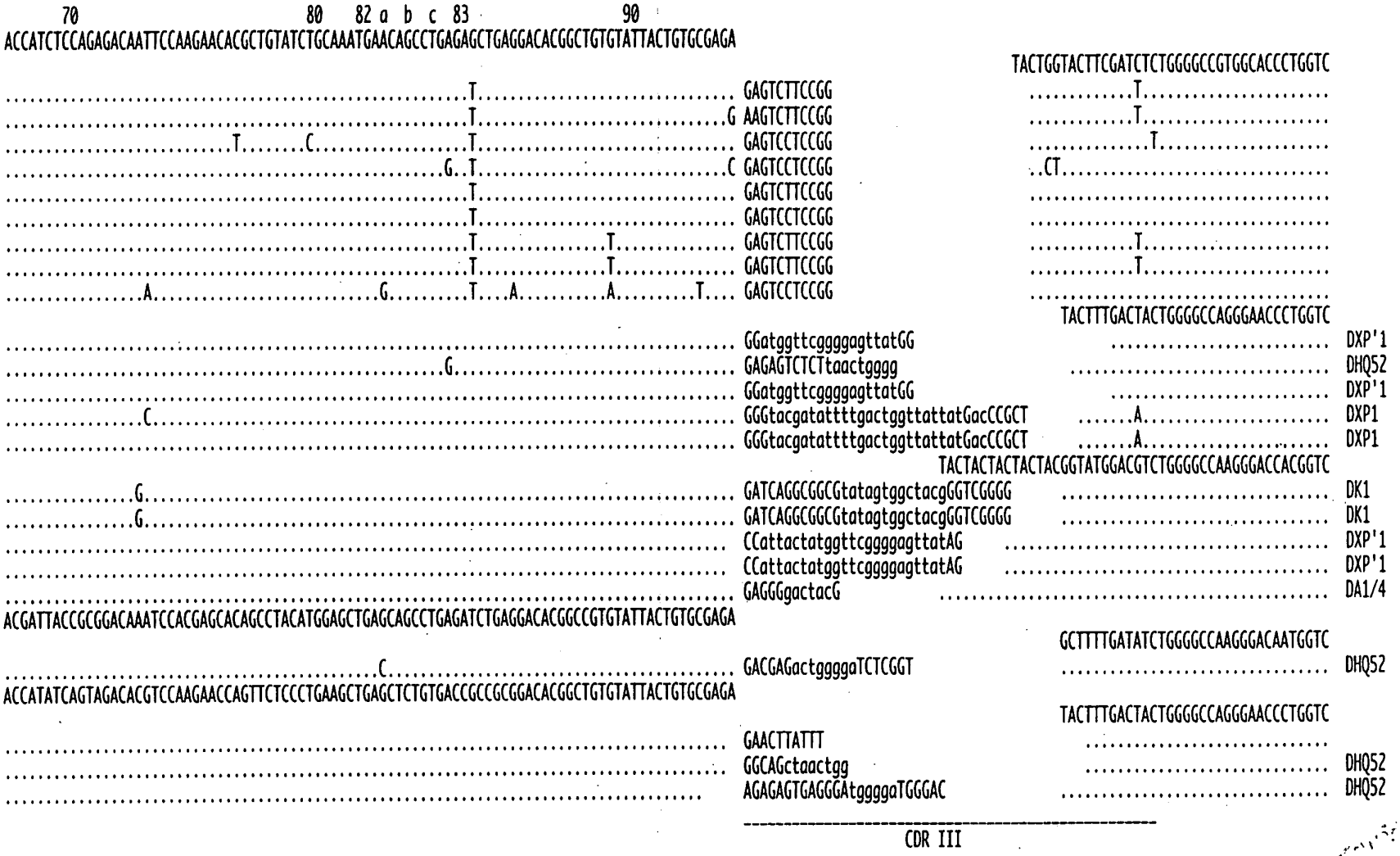

70
80
82 a b c 83
90
ACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAGA
TACTGGTACTTCGATCTCTGGGGCCGTGGCACCCTGGTC
GAGTCTTCCGG
AAGTCTTCCGG
GAGTCCTCCGG
GAGTCCTCCGG
GAGTCTTCCGG
GAGTCCTCCGG
GAGTCTTCCGG
GAGTCTTCCGG
GAGTCCTCCGG
TACTTTGACTACTGGGGCCAGGGAACCCTGGTC
GGatggttcggggagttatGG
GAGAGTCTCTtaactgggg
GGatggttcggggagttatGG
GGGtacgatattttgactggttattatGacCCGCT
GGGtacgatattttgactggttattatGacCCGCT
TACTACTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTC
GATCAGGCGGCGtatagtggctacgGGTCGGGG
GATCAGGCGGCGtatagtggctacgGGTCGGGG
CCattactatggttcggggagttatAG
CCattactatggttcggggagttatAG
GAGGGgactacG
DXP'1
DHQ52
DXP'1
DXP1
DXP1
DK1
DK1
DXP'1
DXP'1
DA1/4
ACGATTACCGCGGACAAATCCACGAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGA
GCTTTTGATATCTGGGGCCAAGGGACAATGGTC
GACGAGactggggaTCTCGGT
DHQ52
ACCATATCAGTAGACACGTCCAAGAACCAGTTCTCCCTGAAGCTGAGCTCTGTGACCGCCGCGGACACGGCTGTGTATTACTGTGCGAGA
TACTTTGACTACTGGGGCCAGGGAACCCTGGTC
GAACTTATTT
GGCAGctaactgg
AGAGAGTGAGGGAtggggaTGGGAC
DHQ52
DHQ52
CDR III

FIG. 68B

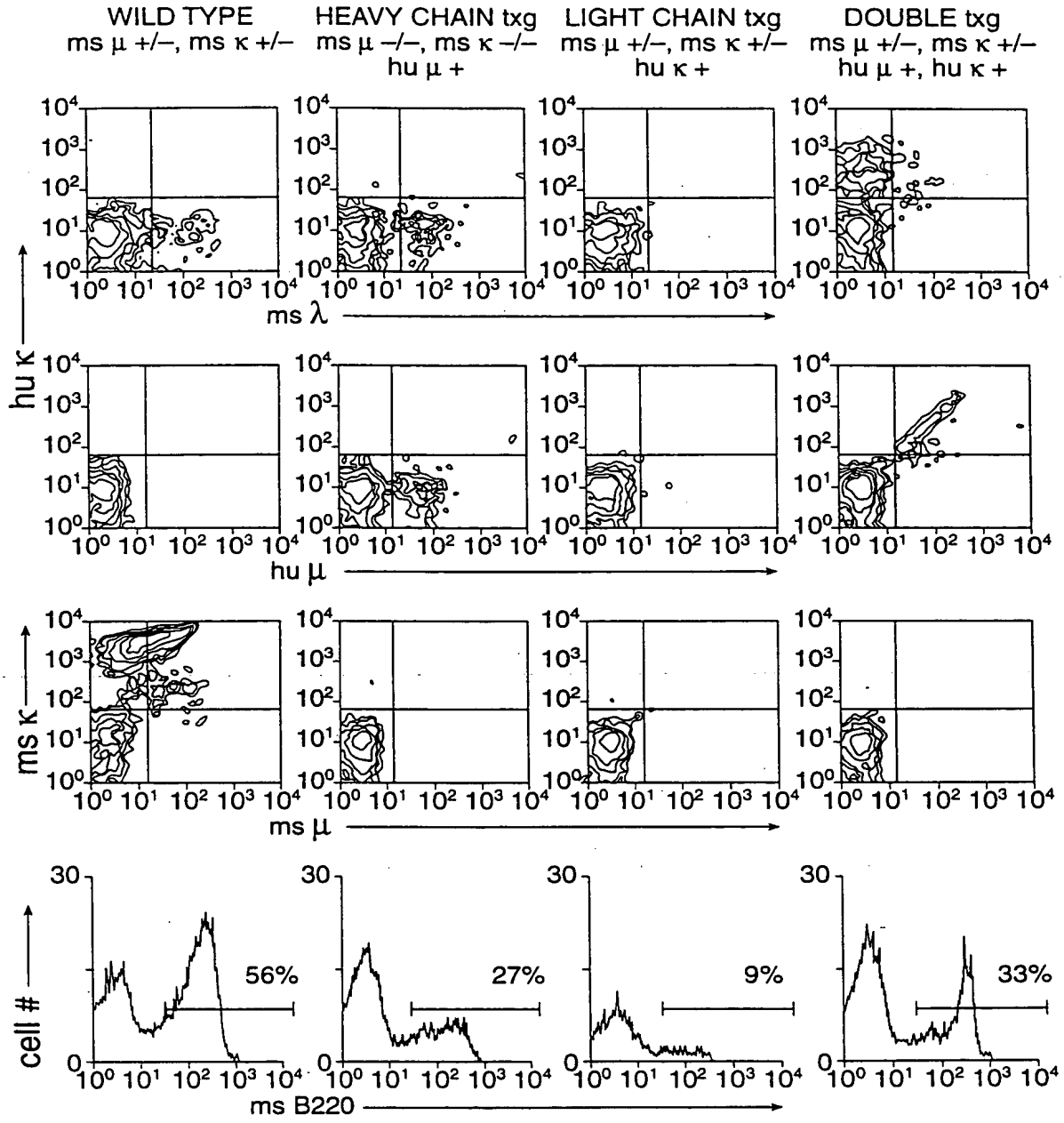

WILD TYPE
ms μ +/–, ms κ +/–
HEAVY CHAIN txg
ms μ –/–, ms κ –/–
hu μ +
LIGHT CHAIN txg
ms μ +/–, ms κ +/–
hu κ +
DOUBLE txg
ms μ +/–, ms κ +/–
hu μ +, hu κ +
ms λ
hu κ
hu μ
ms κ
ms μ
cell #
56%
27%
9%
33%
ms B220

FIG. 69

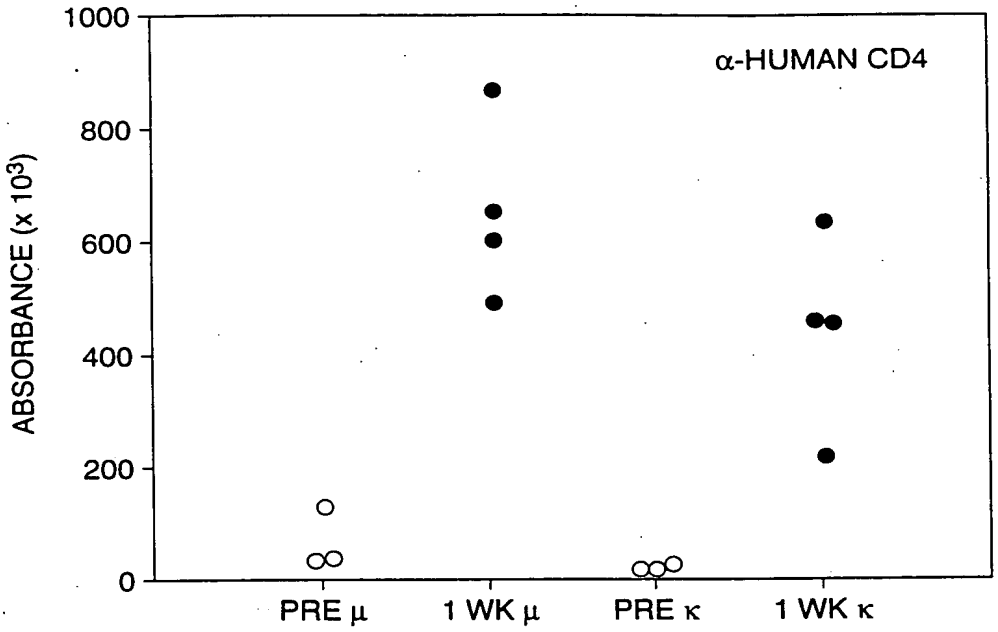


FIG. 71A

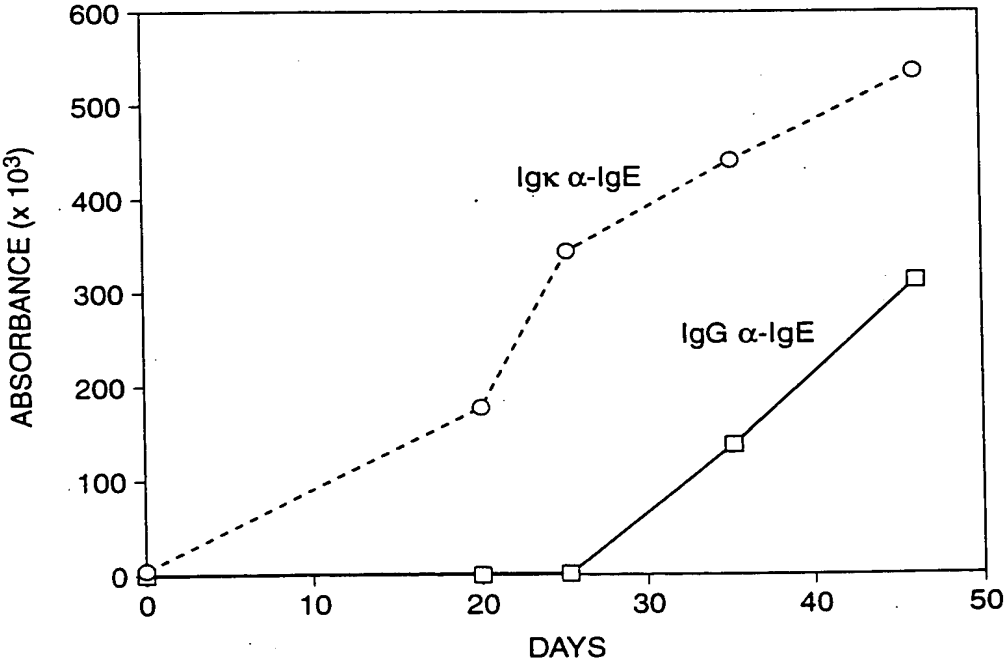


FIG. 71B

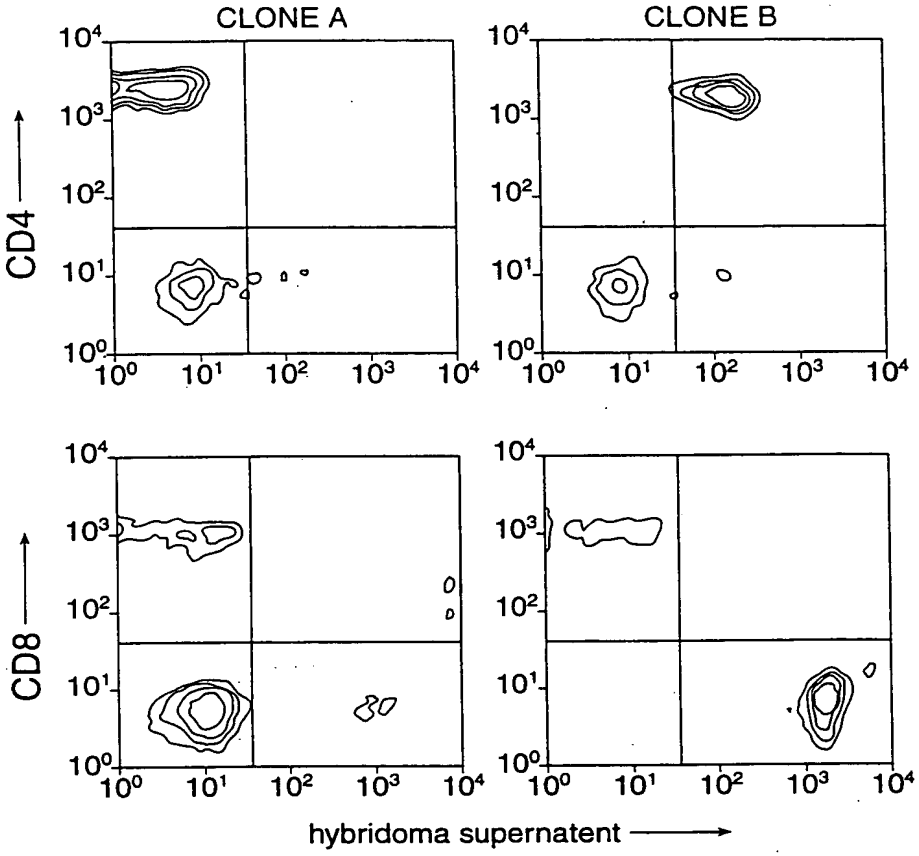

CLONE A
CLONE B
CD4
CD8
10^0
10^1
10^2
10^3
10^4
hybridoma supernatent

FIG. 72

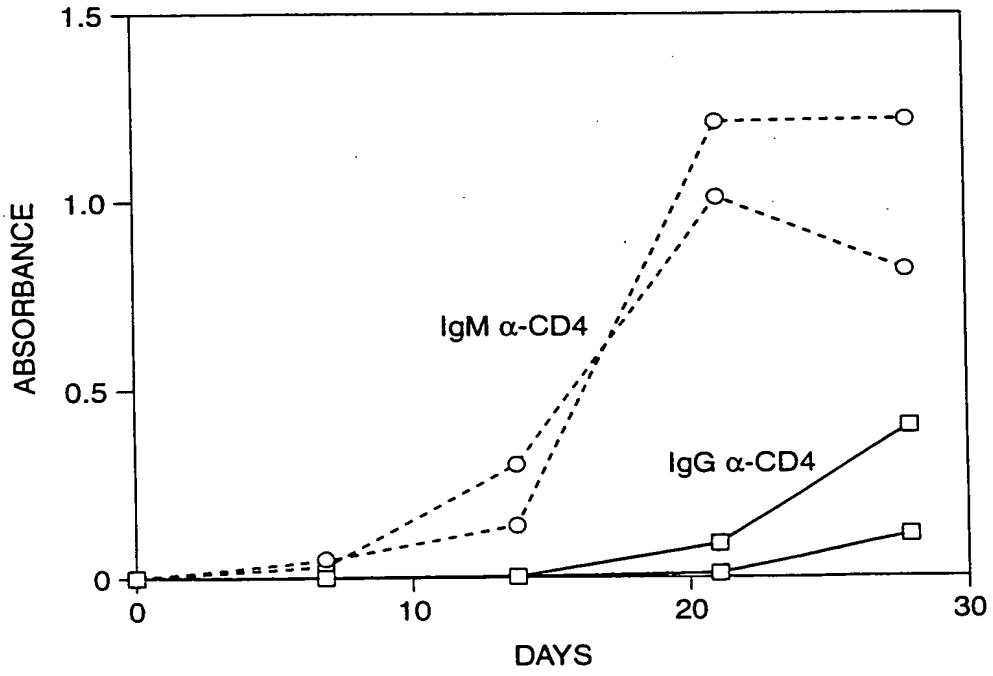
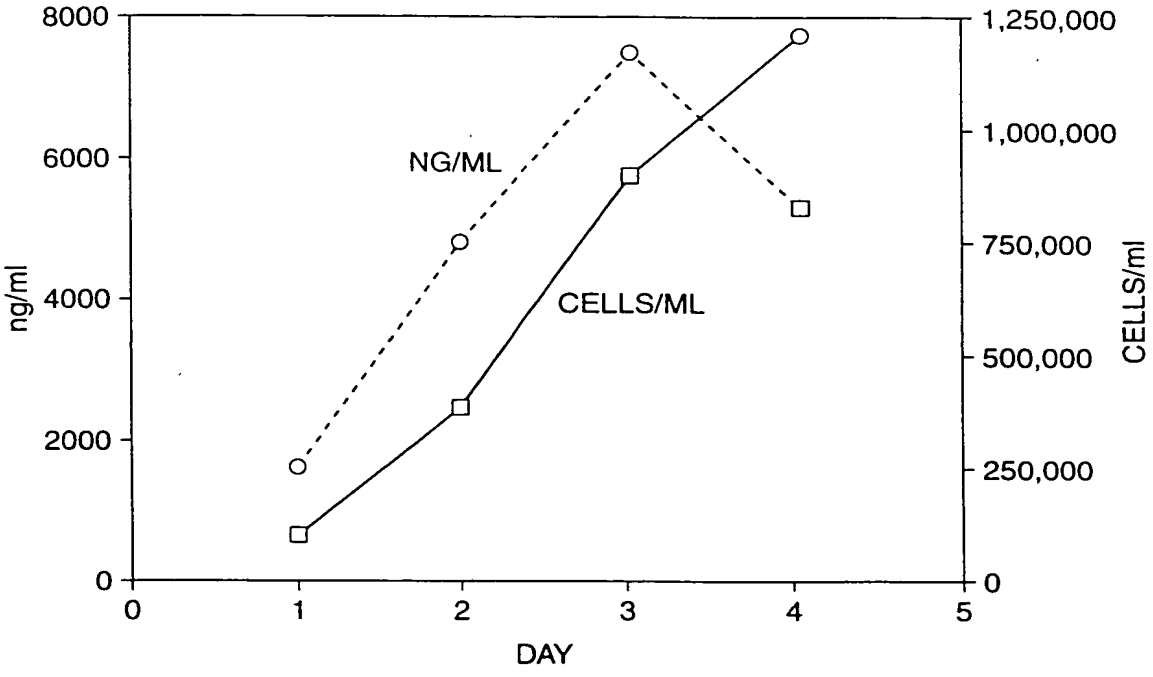

ABSORBANCE
1.5
1.0
0.5
0
IgM α-CD4
IgG α-CD4
0
10
20
30
DAYS

FIG. 73


8000
6000
4000
2000
0
ng/ml
NG/ML
CELLS/ML
1,250,000
1,000,000
750,000
500,000
250,000
0
CELLS/ml
0
1
2
3
4
5
DAY

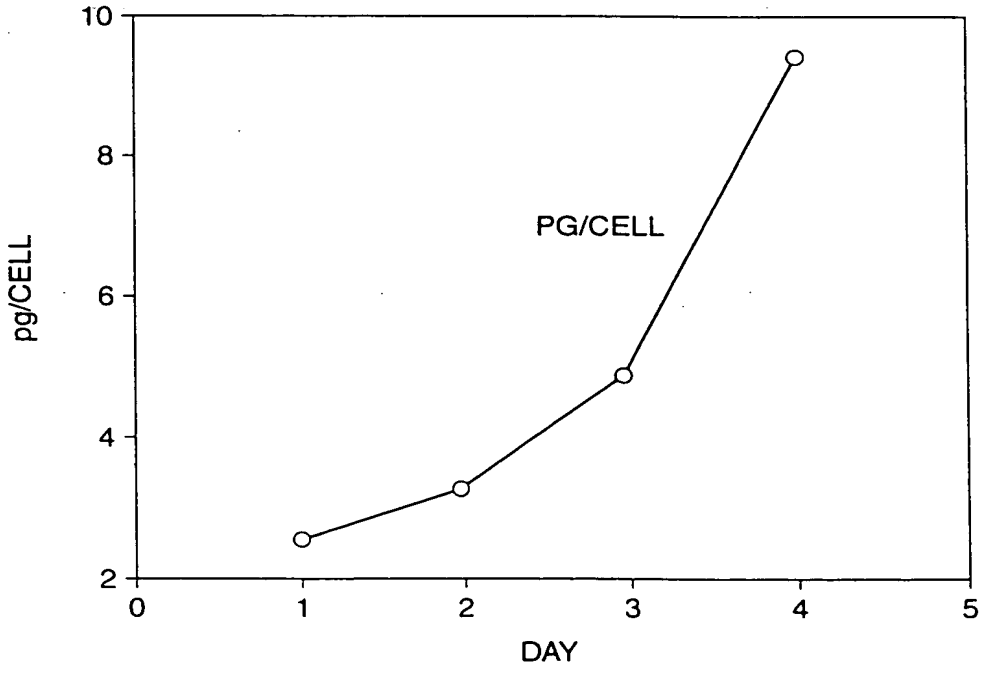
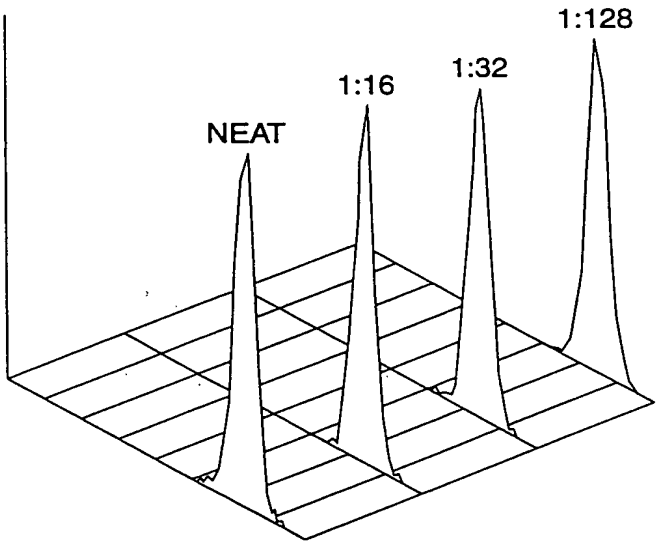

10
8
6
4
2
pg/CELL
PG/CELL
0
1
2
3
4
5
DAY

FIG. 74

RPA-T4/2C11-8
#12:BDPHARMCOMP004\FL2-H\FL2-HEIGHT



Leu-3a/2C11-8
#12:BDPHARMCOMP025\FL2-H\FL2-HEIGHT

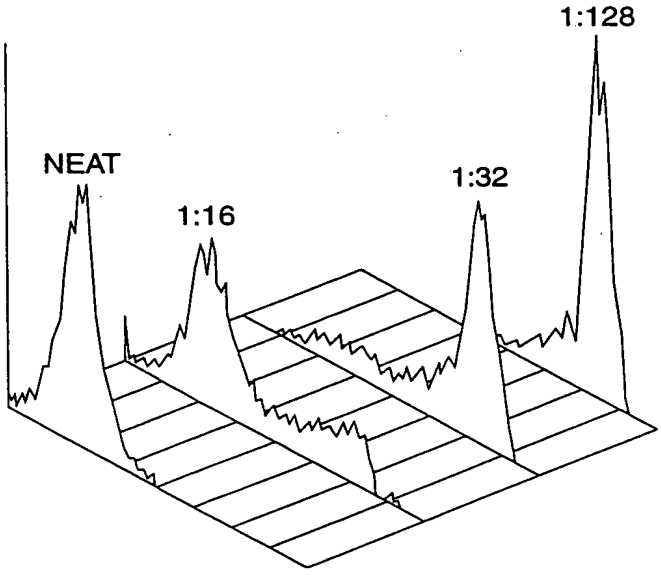


FIG. 75

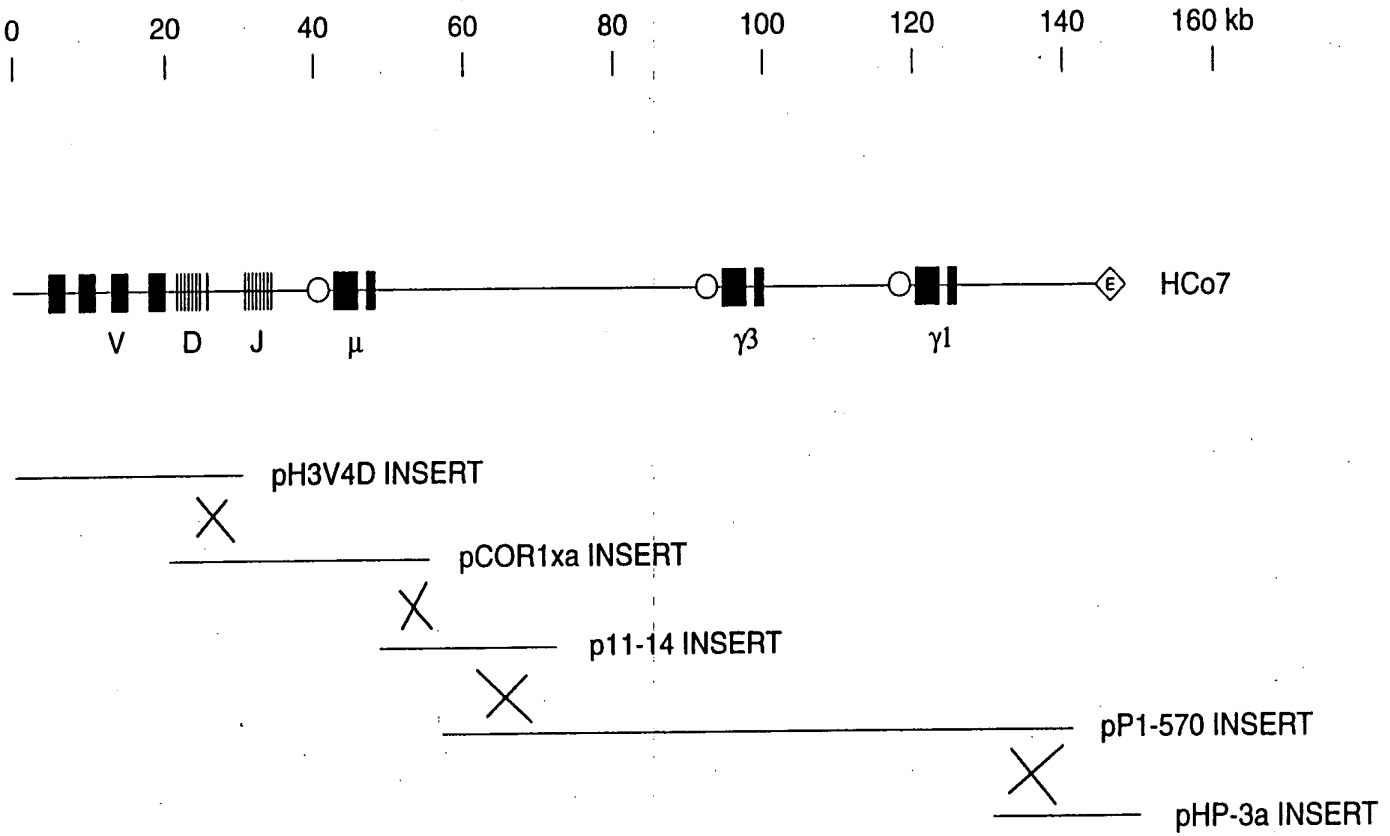

0
20
40
60
80
100
120
140
160 kb
V
D
J
μ
γ3
γ1
HCo7
pH3V4D INSERT
pCOR1xa INSERT
p11-14 INSERT
pP1-570 INSERT
pHP-3a INSERT

FIG. 76

pGP2b sequence:

AATTAGCggccgctgtcgacaagcttcgaattcagtatcgatgtggtacctggatcctcgagtgcGGCCGCAGTATGCAA
AAAAAAGCCCGCTCATTAGGCGGGCTCTTGGCAGAACATATCCATCGCGTCCGCCATCTCCAGCAGCCGCACGCGGCGCA
TCTCGGGCAGCGTTGGGTCCTGGCCACGGGTGCGCATGATCGTGCTCCTGTCGTTGAGGACCCGGCTAGGCTGGCGGGGT
TGCCTTACTGGTTAGCAGAATGAATCACCGATACGCGAGCGAACGTGAAGCGACTGCTGCTGCAAAACGTCTGCGACCTG
AGCAACAACATGAATGGTCTTCGGTTTCCGTGTTTCGTAAAGTCTGGAAACGCGGAAGTCAGCGCCCTGCACCATTATGT
TCCGGATCTGCATCGCAGGATGCTGCTGGCTACCCTGTGGAACACCTACATCTGTATTAACGAAGCGCTGGCATTGACCC
TGAGTGATTTTTCTCTGGTCCCGCCGCATCCATACCGCCAGTTGTTTACCCTCACAACGTTCCAGTAACCGGGCATGTTC
ATCATCAGTAACCCGTATCGTGAGCATCCTCTCTCGTTTCATCGGTATCATTACCCCCATGAACAGAAATTCCCCCTTAC
ACGGAGGCATCAAGTGACCAAACAGGAAAAAACCGCCCTTAACATGGCCCGCTTTATCAGAAGCCAGACATTAACGCTTC
TGGAGAAACTCAACGAGCTGGACGCGGATGAACAGGCAGACATCTGTGAATCGCTTCACGACCACGCTGATGAGCTTTAC
CGCAGCTGCCTCGCGCGTTTCGGTGATGACGGTGAAAACCTCTGACACATGCAGCTCCCGGAGACGGTCACAGCTTGTCT
GTAAGCGGATGCCGGGAGCAGACAAGCCCGTCAGGGCGCGTCAGCGGGTGTTGGCGGGTGTCGGGGCGCAGCCATGACCC
AGTCACGTAGCGATAGCGGAGTGTATACTGGCTTAACTATGCGGCATCAGAGCAGATTGTACTGAGAGTGCACCATATGC
GGTGTGAAATACCGCACAGATGCGTAAGGAGAAAATACCGCATCAGGCGCTCTTCCGCTTCCTCGCTCACTGACTCGCTG
CGCTCGGTCGTTCGGCTGCGGCGAGCGGTATCAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGAATCAGGGGATAA
CGCAGGAAAGAACATGTGAGCAAAAGGCCAGCAAAAGGCCAGGAACCGTAAAAAGGCCGCGTTGCTGGCGTTTTTCCATA
GGCTCCGCCCCCCTGACGAGCATCACAAAAATCGACGCTCAAGTCAGAGGTGGCGAAACCCGACAGGACTATAAAGATAC
CAGGCGTTTCCCCCTGGAAGCTCCCTCGTGCGCTCTCCTGTTCCGACCCTGCCGCTTACCGGATACCTGTCCGCCTTTCT
CCCTTCGGGAAGCGTGGCGCTTTCTCATAGCTCACGCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGCTCCAAGCTGG
GCTGTGTGCACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCCGGTAACTATCGTCTTGAGTCCAACCCGGTAAGA
CACGACTTATCGCCACTGGCAGCAGCCAggcgcgccttggcctaagaggccaCTGGTAACAGGATTAGCAGAGCGAGGTA
TGTAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGCCTAACTACGGCTACACTAGAAGGACAGTATTTGGTATCTGCGCTC
TGCTGAAGCCAGTTACCTTCGGAAAAAGAGTTGGTAGCTCTTGATCCGGCAAACAAACCACCGCTGGTAGCGGTGGTTTT
TTTGTTTGCAAGCAGCAGATTACGCGCAGAAAAAAAGGATCTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGC
TCAGTGGAACGAAAACTCACGTTAAGGGATTTTGGTCATGAGATTATCAAAAAGGATCTTCACCTAGATCCTTTTAAATT
AAAAATGAAGTTTTAAATCAATCTAAAGTATATATGAGTAAACTTGGTCTGACAGTTACCAATGCTTAATCAGTGAGGCA
CCTATCTCAGCGATCTGTCTATTTCGTTCATCCATAGTTGCCTGACTCCCCGTCGTGTAGATAACTACGATACGGGAGGG
CTTACCATCTGGCCCCAGTGCTGCAATGATACCGCGAGACCCACGCTCACCGGCTCCAGATTTATCAGCAATAAACCAGC
CAGCCGGAAGGGCCGAGCGCAGAAGTGGTCCTGCAACTTTATCCGCCTCCATCCAGTCTATTAATTGTTGCCGGGAAGCT
AGAGTAAGTAGTTCGCCAGTTAATAGTTTGCGCAACGTTGTTGCCATTGCTGCAGGCATCGTGGTGTCACGCTCGTCGTT
TGGTATGGCTTCATTCAGCTCCGGTTCCCAACGATCAAGGCGAGTTACATGATCCCCCATGTTGTGCAAAAAAGCGGTTA
GCTCCTTCGGTCCTCCGATCGTTGTCAGAAGTAAGTTGGCCGCAGTGTTATCACTCATGGTTATGGCAGCACTGCATAAT
TCTCTTACTGTCATGCCATCCGTAAGATGCTTTTCTGTGACTGGTGAGTACTCAACCAAGTCATTCTGAGAATAGTGTAT
GCGGCGACCGAGTTGCTCTTGCCCGGCGTCAACACGGGATAATACCGCGCCACATAGCAGAACTTTAAAAGTGCTCATCA
TTGGAAAACGTTCTTCGGGGCGAAAACTCTCAAGGATCTTACCGCTGTTGAGATCCAGTTCGATGTAACCCACTCGTGCA
CCCAACTGATCTTCAGCATCTTTTACTTTCACCAGCGTTTCTGGGTGAGCAAAAACAGGAAGGCAAAATGCCGCAAAAAA
GGGAATAAGGGCGACACGGAAATGTTGAATACTCATACTCTTCCTTTTTCAATATTATTGAAGCATTTATCAGGGTTATT
GTCTCATGAGCGGATACATATTTGAATGTATTTAGAAAAATAAACAAATAGGGGTTCCGCGCACATTTCCCCGAAAAGTG
CCACCTGACGTCTAAGAAACCATTATTATCATGACATTAACCTATAAAAATAGGCGTATCACGAGGCCCTTTCGTCTTCA
AG

FIG. 77A

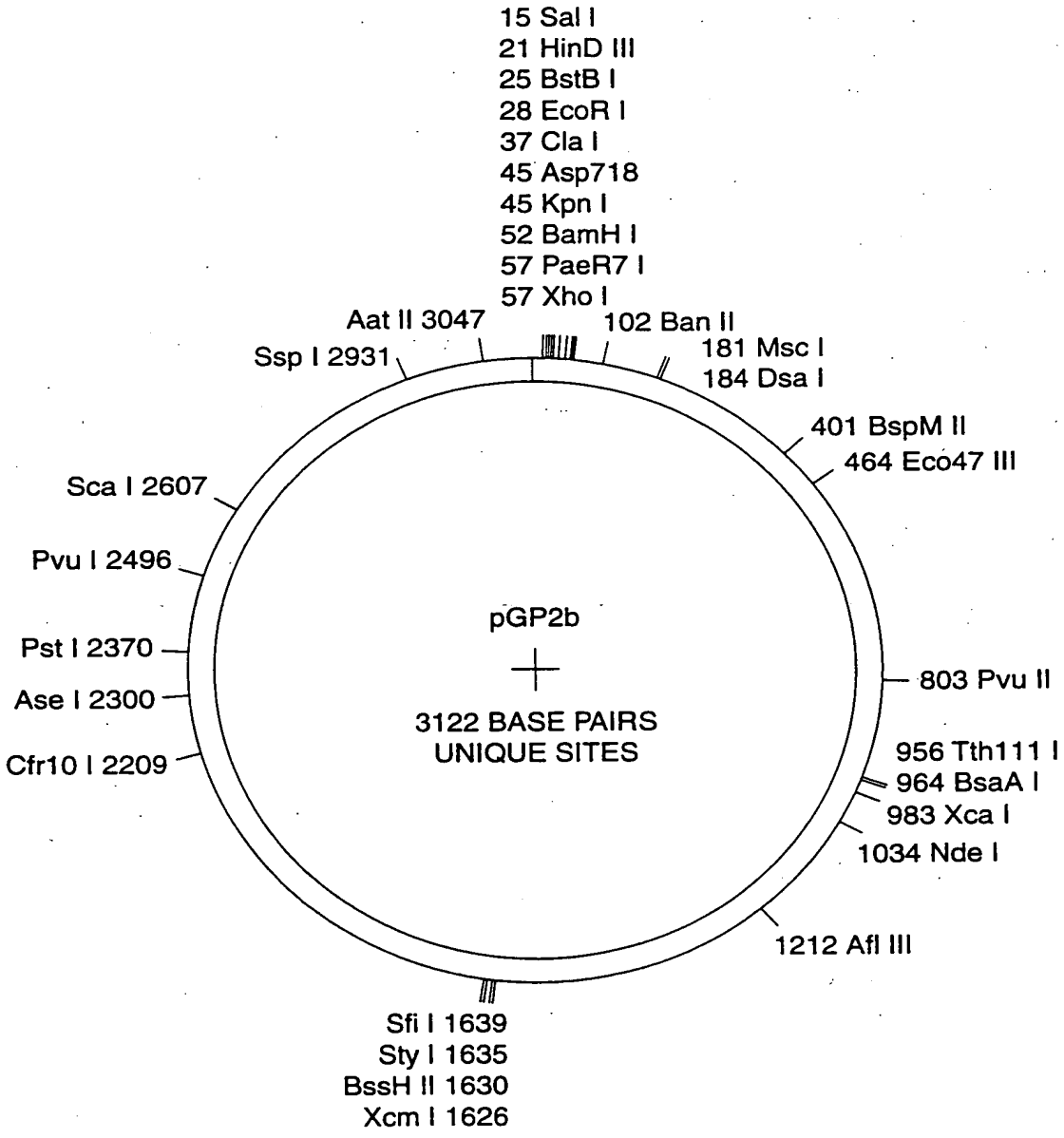

15 Sal I
21 HinD III
25 BstB I
28 EcoR I
37 Cla I
45 Asp718
45 Kpn I
52 BamH I
57 PaeR7 I
57 Xho I
Aat II 3047
102 Ban II
Ssp I 2931
181 Msc I
184 Dsa I
401 BspM II
464 Eco47 III
Sca I 2607
Pvu I 2496
pGP2b
Pst I 2370
Ase I 2300
3122 BASE PAIRS
UNIQUE SITES
803 Pvu II
Cfr10 I 2209
956 Tth111 I
964 BsaA I
983 Xca I
1034 Nde I
1212 Afl III
Sfi I 1639
Sty I 1635
BssH II 1630
Xcm I 1626

FIG. 77B

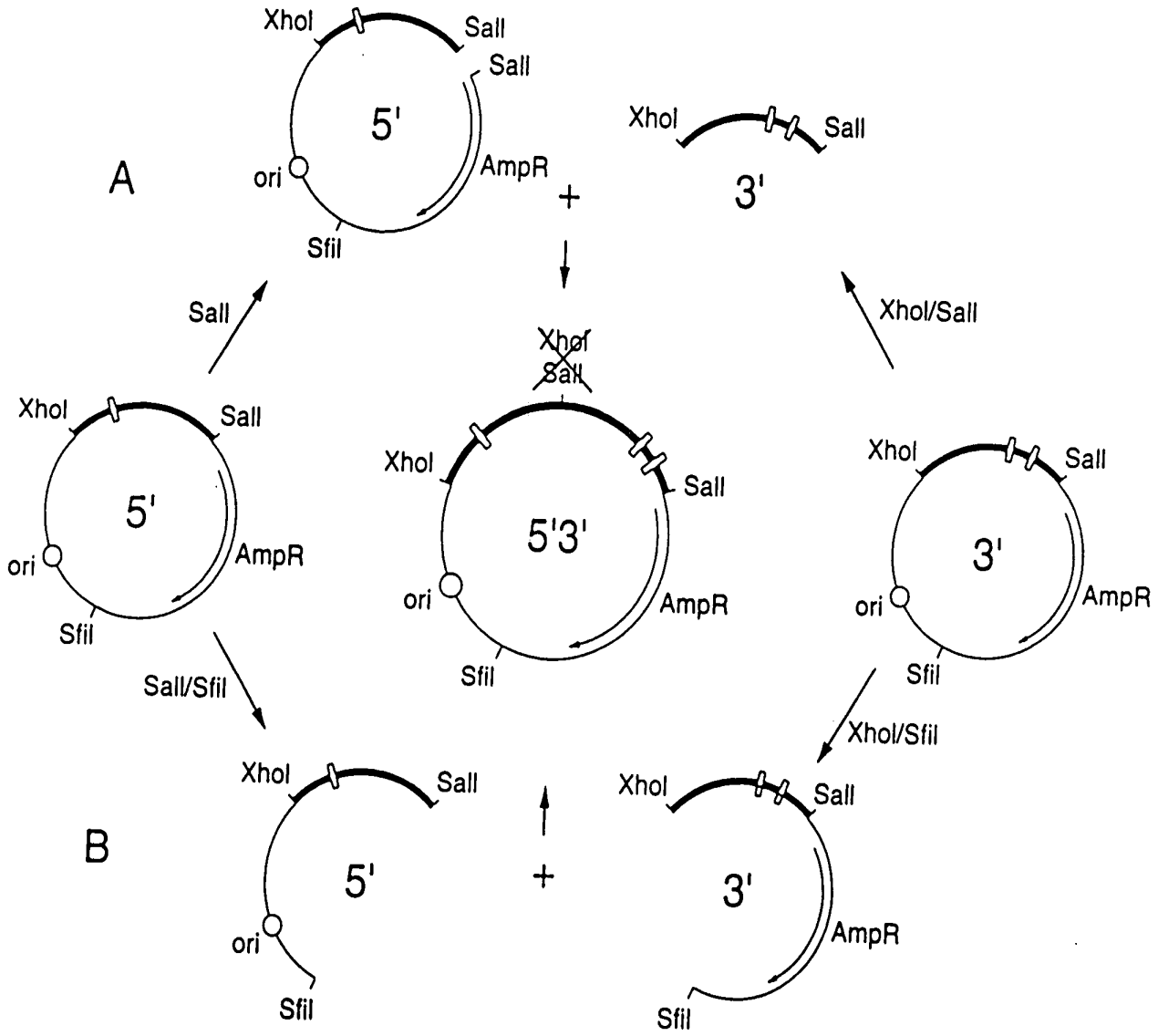


FIG. 78

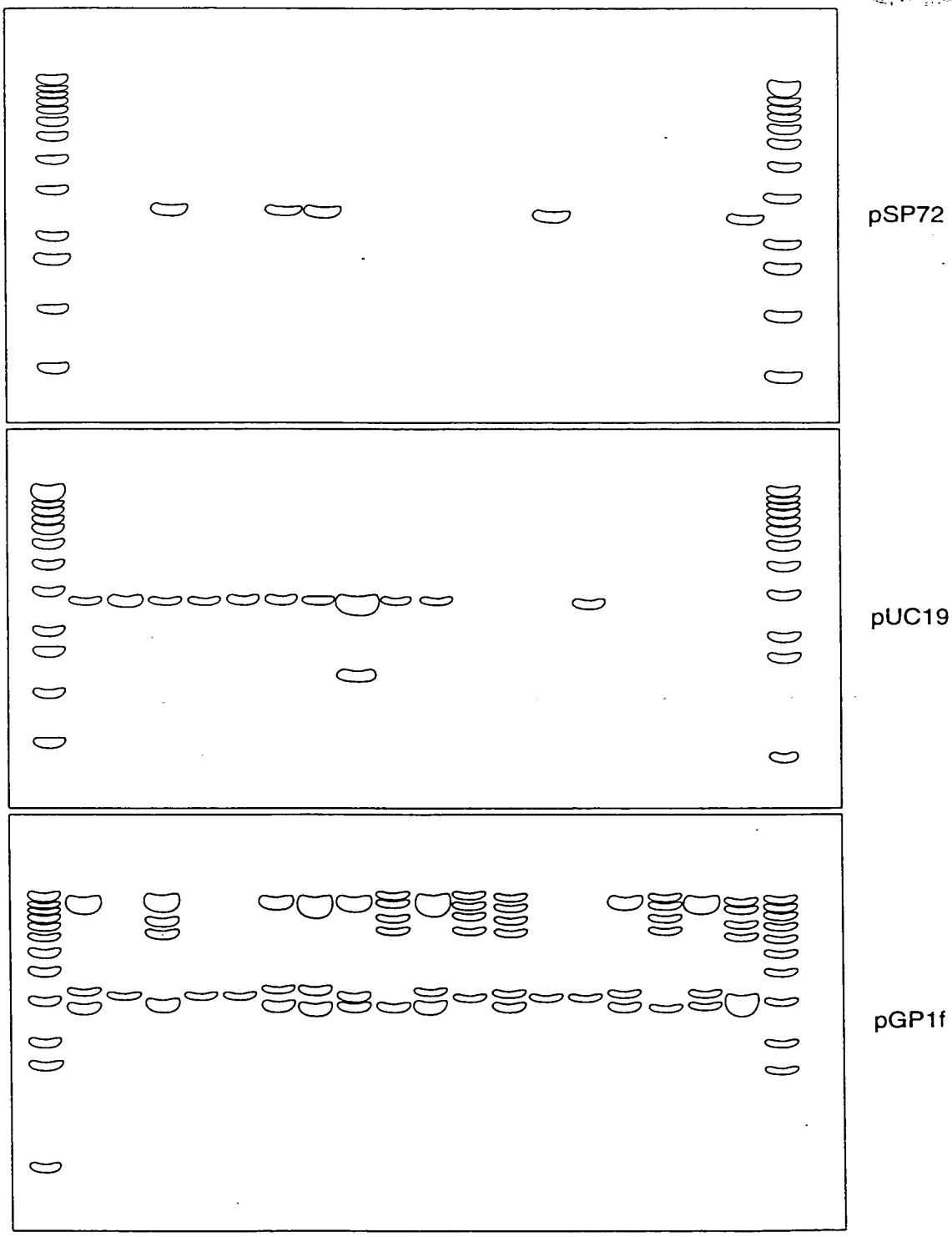


FIG. 79

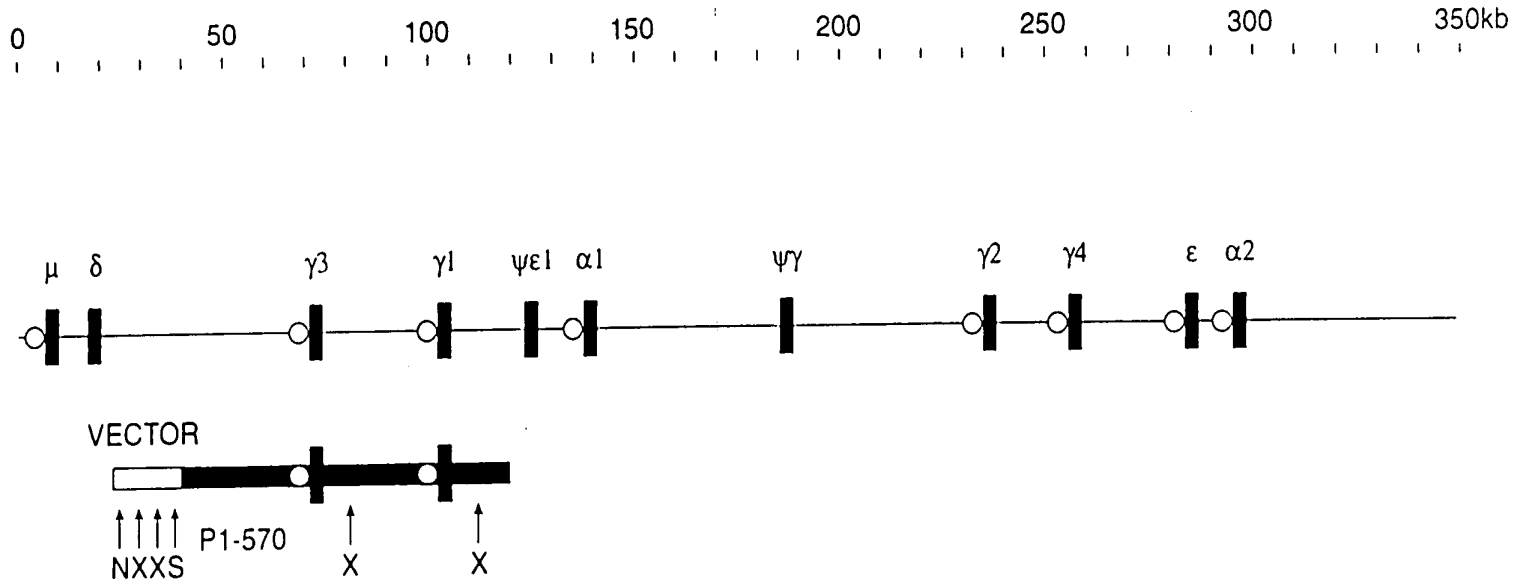

0
50
100
150
200
250
300
350kb
μ
δ
γ3
γ1
ψε1
α1
ψγ
γ2
γ4
ε
α2
VECTOR
P1-570
NXXS
X
X

FIG. 80

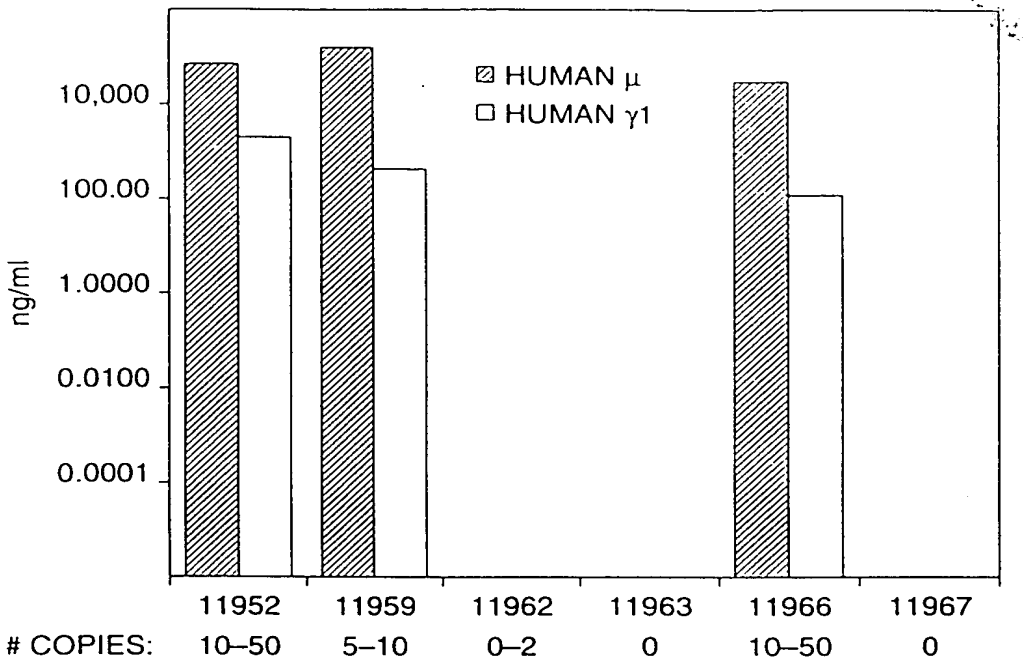

HUMAN μ
HUMAN γ1
10,000
100.00
1.0000
0.0100
0.0001
ng/ml
11952
11959
11962
11963
11966
11967
COPIES:
10–50
5–10
0–2
0
10–50
0

FIG. 81

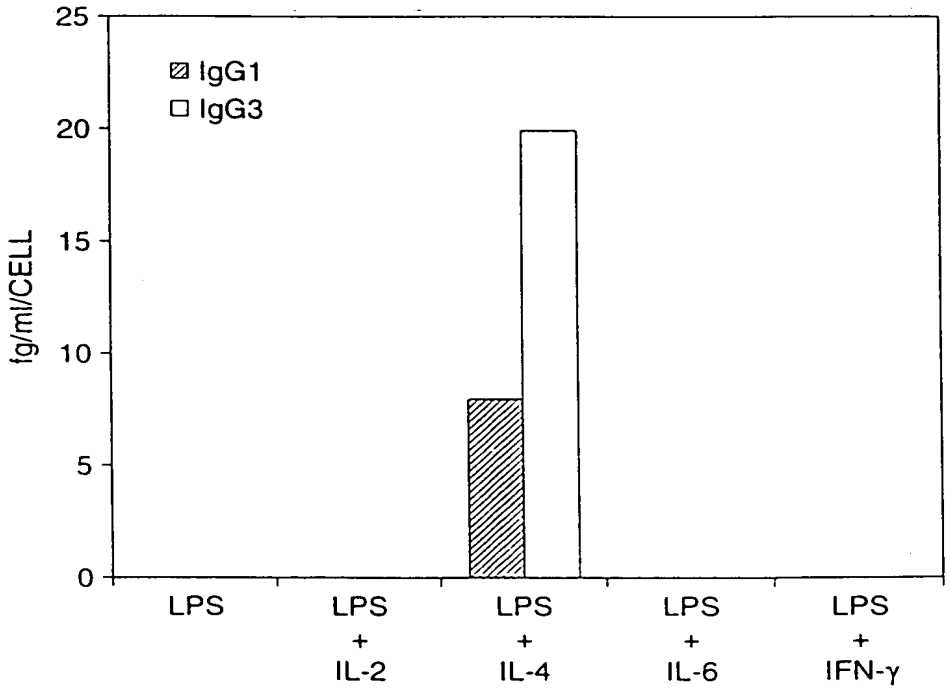

IgG1
IgG3
25
20
15
10
5
0
fg/ml/CELL
LPS
LPS + IL-2
LPS + IL-4
LPS + IL-6
LPS + IFN-γ

FIG. 84

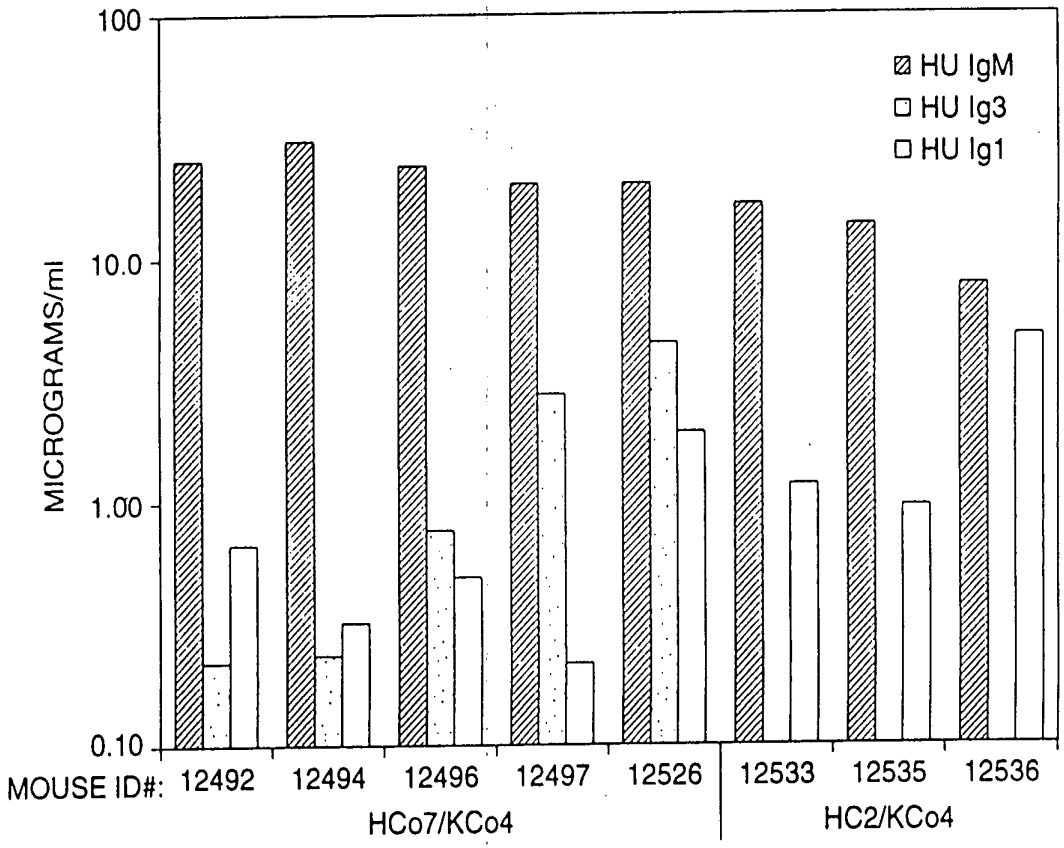

100
10.0
1.00
0.10
MICROGRAMS/ml
HU IgM
HU Ig3
HU Ig1
MOUSE ID#: 12492 12494 12496 12497 12526 12533 12535 12536
HCo7/KCo4
HC2/KCo4

FIG. 82

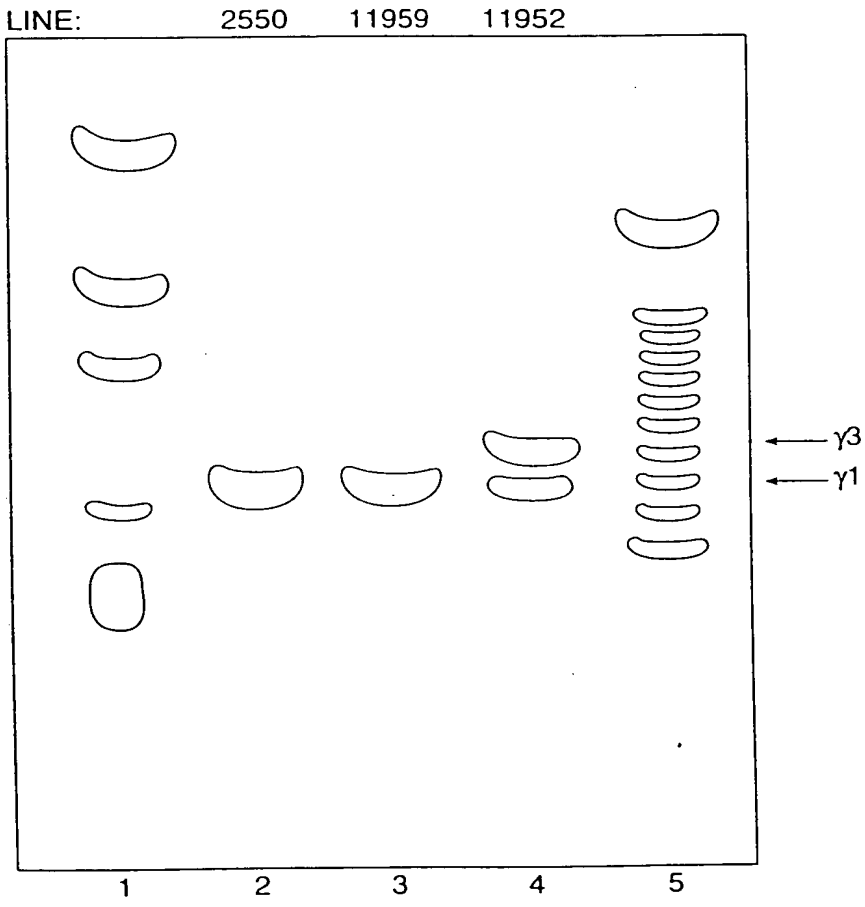


FIG. 83

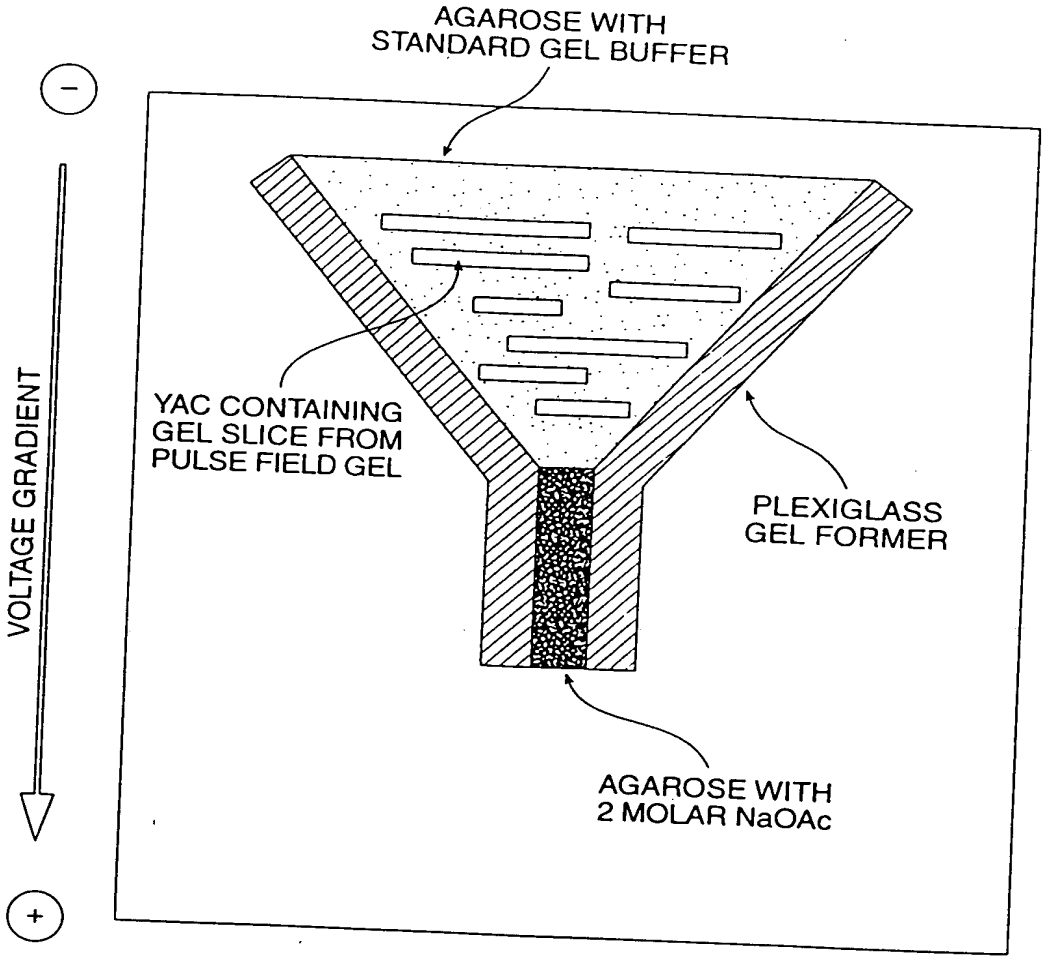

AGAROSE WITH
STANDARD GEL BUFFER
YAC CONTAINING
GEL SLICE FROM
PULSE FIELD GEL
PLEXIGLASS
GEL FORMER
AGAROSE WITH
2 MOLAR NaOAc
VOLTAGE GRADIENT
−
+

FIG. 85

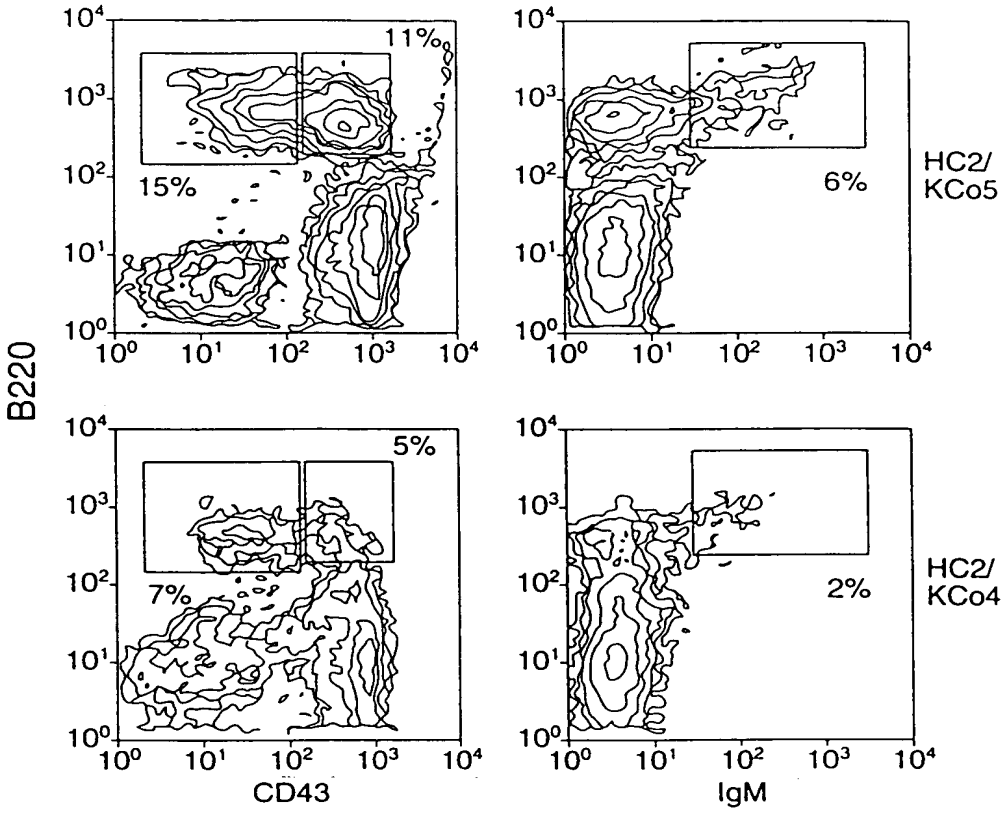

B220
11%
15%
6%
HC2/
KCo5
5%
7%
2%
HC2/
KCo4
CD43
IgM

FIG. 86

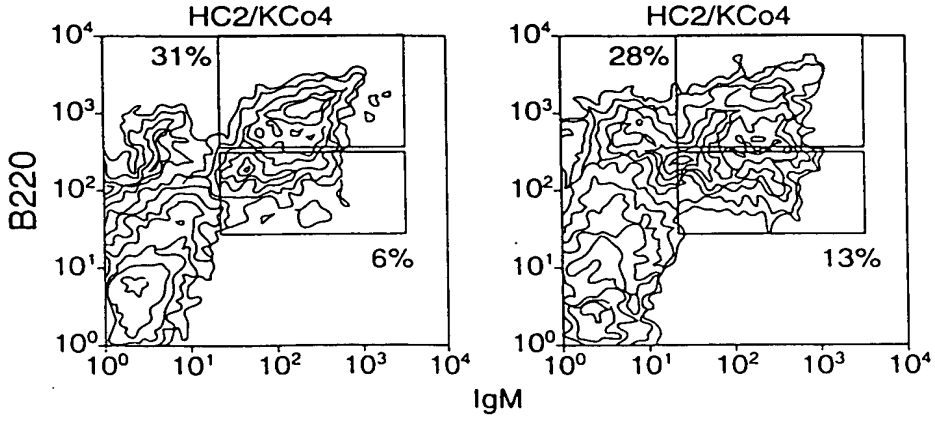

HC2/KCo4
HC2/KCo4
B220
31%
6%
28%
13%
IgM

FIG. 87

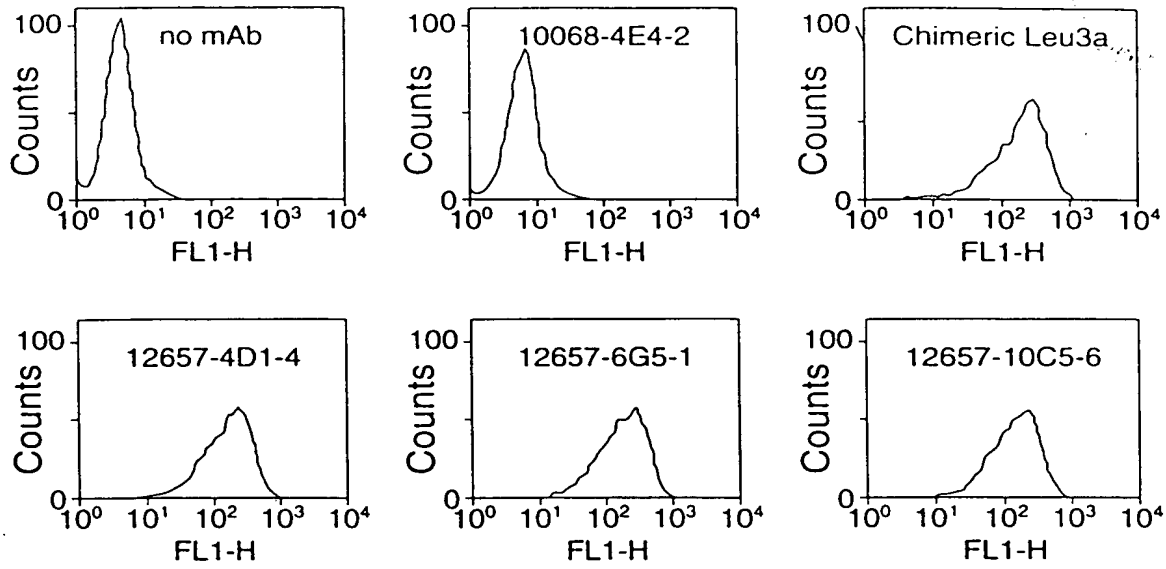

no mAb
10068-4E4-2
Chimeric Leu3a
12657-4D1-4
12657-6G5-1
12657-10C5-6
Counts
FL1-H
100
0
10^0 10^1 10^2 10^3 10^4

FIG. 88

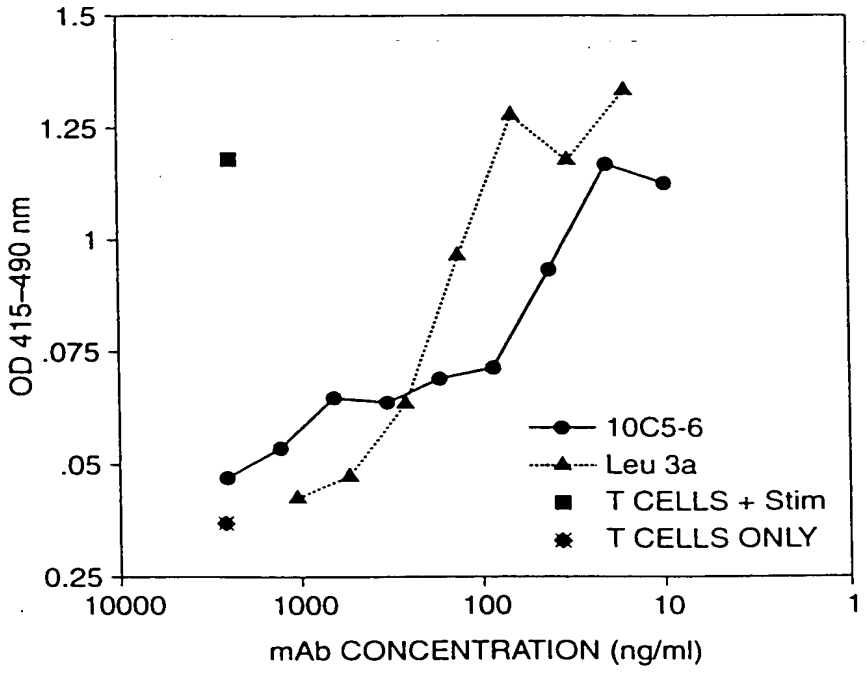

1.5
1.25
1
.075
.05
0.25
OD 415–490 nm
10000
1000
100
10
1
mAb CONCENTRATION (ng/ml)
10C5-6
Leu 3a
T CELLS + Stim
T CELLS ONLY

FIG. 90

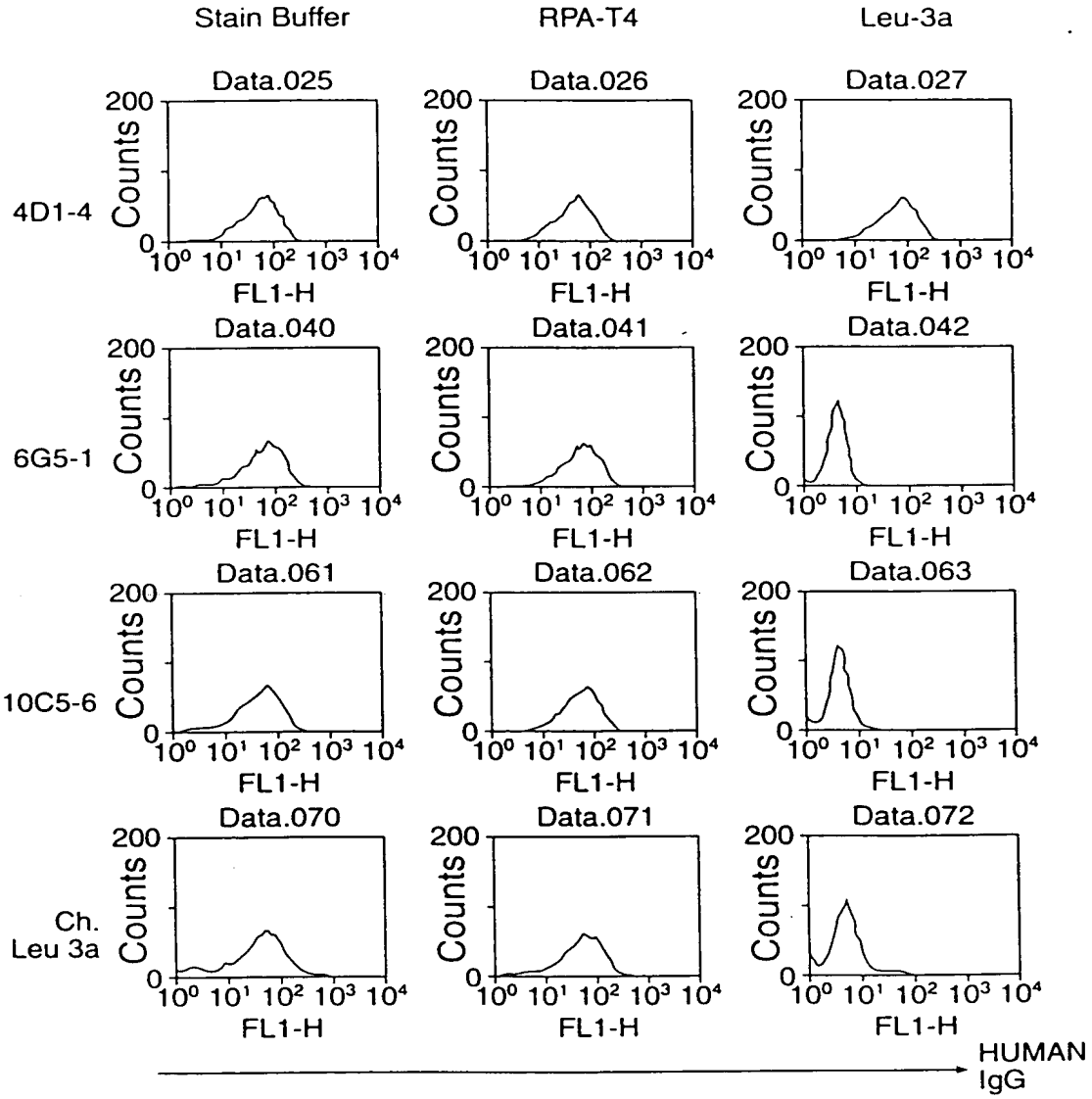

Stain Buffer
RPA-T4
Leu-3a
Data.025
Data.026
Data.027
4D1-4
Data.040
Data.041
Data.042
6G5-1
Data.061
Data.062
Data.063
10C5-6
Data.070
Data.071
Data.072
Ch. Leu 3a
Counts
200
0
10^0 10^1 10^2 10^3 10^4
FL1-H
HUMAN IgG

FIG. 89